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Request for grant of a patent

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14AUG02 E740857-1 D02639
P01/7700 0.00-0218874.6

Your reference	T1569PV
Patent application number (The Patent Office will fill in this part)	0218874.6 — 13 AUG 2002
Full name, address and postcode of the or of each applicant (underline all surnames)	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
Patents ADP number (if you know it)	00597799001
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
Title of the invention	Therapeutic agents
Name of your agent (if you have one)	Dr. J. Thompson
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road Harlow Essex CM20 2QR
Patents ADP number (if you know it)	4392742002

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If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

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a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
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Yes

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Statement of inventorship and right to grant of a patent (Patents Form 7/77)	-
Request for preliminary examination and search (Patents Form 9/77)	-
Request for substantive examination (Patents Form 10/77)	-
Any other documents (please specify)	-

I. I/We request the grant of a patent on the basis of this application.

Signature J. Thompson Date 12 August, 2002

Dr. J. Thompson

2. Name and daytime telephone number of person to contact in the United Kingdom — Dr. J. Thompson — 01279 440172

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THERAPEUTIC AGENTS

The present invention relates to a class of substituted pyridazine derivatives and to their use in therapy. More particularly, this invention is concerned with 4-phenylpyridazine analogues. These compounds are ligands for $GABA_A$ receptors and are therefore useful in the therapy of deleterious neurological complaints.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors, which are members of the ligand-gated ion channel superfamily; and (2) $GABA_B$ receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual $GABA_A$ receptor subunits were cloned the number of known members of the mammalian family has grown to include at least six α subunits, four β subunits, three γ subunits, one δ subunit, one ε subunit and two ρ subunits.

Although knowledge of the diversity of the $GABA_A$ receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional $GABA_A$ receptor expressed by transiently transfecting cDNAs into cells. As indicated above, δ, ε and ρ subunits also exist, but are present only to a minor extent in $GABA_A$ receptor populations.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native $GABA_A$ receptor exists in pentameric form. The selection of at least one α, one β and one γ subunit from a repertoire of seventeen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional permutations that would be possible if the arrangement of subunits

around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include, amongst many others, $\alpha1\beta2\gamma2$, $\alpha2\beta\gamma1$, $\alpha2\beta2/3\gamma2$, $\alpha3\beta\gamma2/3$, $\alpha4\beta\delta$, $\alpha5\beta3\gamma2/3$, $\alpha6\beta\gamma2$ and $\alpha6\beta\delta$. Subtype assemblies containing an $\alpha1$ subunit are present in most areas of the brain and are thought to account for over 40% of $GABA_A$ receptors in the rat. Subtype assemblies containing $\alpha2$ and $\alpha3$ subunits respectively are thought to account for about 25% and 17% of $GABA_A$ receptors in the rat. Subtype assemblies containing an $\alpha5$ subunit are expressed predominantly in the hippocampus and cortex and are thought to represent about 4% of $GABA_A$ receptors in the rat.

A characteristic property of all known $GABA_A$ receptors is the presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored of the $GABA_A$ receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the $GABA_A$ receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a $GABA_A$ receptor comprising the $\alpha1$ subunit in combination with a β subunit and $\gamma2$. This is the most abundant $GABA_A$ receptor subtype, and is believed to represent almost half of all $GABA_A$ receptors in the brain.

Two other major populations are the $\alpha2\beta\gamma2$ and $\alpha3\beta\gamma2/3$ subtypes. Together these constitute approximately a further 35% of the total $GABA_A$ receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha5$-containing subtype assemblies. The physiological role of these subtypes has hitherto been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha1\beta\gamma2$, $\alpha2\beta\gamma2$ or $\alpha3\beta\gamma2$ subtypes will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the $GABA_A$ receptor by acting as BZ agonists are referred to hereinafter as "$GABA_A$ receptor agonists". The $\alpha1$-selective $GABA_A$ receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through $GABA_A$ receptors containing the $\alpha1$ subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which interact more favourably with the $\alpha2$ and/or $\alpha3$ subunit than with $\alpha1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Moreover, agents which are inverse agonists of the $\alpha5$ subunit are likely to be beneficial in enhancing cognition, for example in subjects suffering from dementing conditions such as Alzheimer's disease. Also, agents which are antagonists or inverse agonists at $\alpha1$ might be employed to reverse sedation or hypnosis caused by $\alpha1$ agonists.

The compounds of the present invention, being selective ligands for $GABA_A$ receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; attention deficit hyperactivity disorder; Tourette's syndrome;

speech disorders, including stuttering; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work.

Further disorders for which selective ligands for $GABA_A$ receptors may be of benefit include pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as motion sickness, and post-operative nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; premenstrual syndrome; muscle spasm or spasticity, e.g. in paraplegic patients; hearing disorders, including tinnitus and age-related hearing impairment; urinary incontinence; and the effects of substance abuse or dependency, including alcohol withdrawal. Selective ligands for $GABA_A$ receptors may be beneficial in enhancing cognition, for example in subjects suffering from dementing conditions such as Alzheimer's disease; and may also be effective as pre-medication prior to anaesthesia or minor procedures such as endoscopy, including gastric endoscopy.

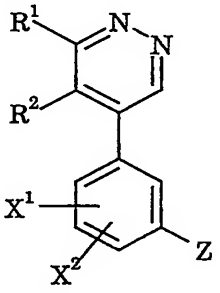
In addition, the compounds in accordance with the present invention may be useful as radioligands in assays for detecting compounds capable of binding to the human $GABA_A$ receptor.

The present invention provides a class of pyridazine derivatives which possess desirable binding properties at various $GABA_A$ receptor subtypes. The compounds in accordance with the present invention have good affinity as ligands for the $\alpha 2$ and/or $\alpha 3$ and/or $\alpha 5$ subunit of the human $GABA_A$ receptor. The compounds of this invention may interact more favourably with the $\alpha 2$ and/or $\alpha 3$ subunit than with the $\alpha 1$ subunit; and/or may interact more favourably with the $\alpha 5$ subunit than with the $\alpha 1$ subunit.

The compounds of the present invention are $GABA_A$ receptor subtype ligands having a binding affinity (K_i) for the $\alpha 2$ and/or $\alpha 3$ and/or $\alpha 5$ subunit, as measured in the assay described hereinbelow, of 200 nM or less, typically of 100 nM or less, and ideally of 20 nM or less. The

compounds in accordance with this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective affinity for the α2 and/or α3 and/or α5 subunit relative to the α1 subunit. However, compounds which are not selective in terms of their binding affinity for the α2 and/or α3 and/or α5 subunit relative to the α1 subunit are also encompassed within the scope of the present invention; such compounds will desirably exhibit functional selectivity in terms of zero or weak (positive or negative) efficacy at the α1 subunit and (i) a full or partial agonist profile at the α2 and/or α3 subunit, and/or (ii) an inverse agonist profile at the α5 subunit.

The present invention provides a compound of formula I, or an *N*-oxide thereof or a pharmaceutically acceptable salt thereof:



(I)

wherein

X^1 represents hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl or C_{1-6} alkoxy;

X^2 represents hydrogen or halogen;

Z represents hydrogen, halogen, cyano, cyanomethyl, trifluoromethyl, nitro, hydroxy, C_{1-6} alkoxy, formyl, C_{2-6} alkoxycarbonyl, or an optionally substituted aryl, heteroaryl or heteroaryl(C_{1-6})alkoxy group;

R^1 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$, $-CONR^aR^b$ or $-CR^a{=}NOR^b$;

R^2 represents hydrogen or C_{2-6} alkoxycarbonyl; and

R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

Where Z in the compounds of formula I above represents aryl, heteroaryl or heteroaryl(C_{1-6})alkoxy, this group may be unsubstituted, or substituted by one or more substituents. Typically, the group Z will be unsubstituted, or substituted by one or two substituents. Typical substituents on the group Z include halogen, cyano, trifluoromethyl, nitro, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, oxy, C_{1-6} alkylsulphonyl, amino, aminocarbonyl, formyl, C_{2-6} alkoxycarbonyl and $-CR^a=NOR^b$, wherein R^a and R^b are as defined above. Illustrative substituents on Z include halogen, cyano, trifluoromethyl and C_{1-6} alkyl.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable

hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl,-indanyl, aryl and aryl(C_{1-6})alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl and heteroaryl(C_{1-6})alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylamino" and "C_{1-6} alkylsulphonyl" are to be construed accordingly.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl and dimethylallyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Typical examples of C_{3-7} cycloalkyl(C_{1-6})alkyl groups include cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

Particular indanyl groups include indan-1-yl and indan-2-yl.

Particular aryl groups include phenyl and naphthyl, preferably phenyl.

Particular aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

A typical heterocycloalkenyl group is dihydropyrrolyl.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C_{1-6})alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, pyrazolylmethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, halogen, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, aminocarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, arylsulphonyl, $-NR^vR^w$, $-NR^vCOR^w$, $-NR^vCO_2R^w$, $-NR^vSO_2R^w$, $-CH_2NR^vSO_2R^w$, $-NHCONR^vR^w$, $-CONR^vR^w$, $-SO_2NR^vR^w$ and $-CH_2SO_2NR^vR^w$, in which R^v and R^w independently represent hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluoro or chloro.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Suitable values for the X^1 substituent include hydrogen, fluoro, chloro, methyl, trifluoromethyl and methoxy; in particular hydrogen or fluoro; and especially fluoro.

Typical values of X^2 include hydrogen and fluoro, especially hydrogen.

Typically, Z represents an optionally substituted aryl or heteroaryl group.

Selected values for the substituent Z include phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl, any of which groups may be optionally substituted by one or more substituents.

In one favoured embodiment, Z represents an optionally substituted phenyl group, in particular monosubstituted or disubstituted phenyl. In another favoured embodiment, Z represents optionally substituted pyridinyl, especially unsubstituted, monosubstituted or disubstituted pyridin-2-yl, pyridin-3-yl or pyridin-4-yl.

Examples of suitable substituents on the group Z include fluoro, chloro, cyano, trifluoromethyl, nitro, methyl, hydroxy, methoxy, oxy, methanesulphonyl, amino, aminocarbonyl, formyl, methoxycarbonyl and -CH=NOH.

Examples of particular substituents on the group Z include fluoro, cyano, trifluoromethyl and methyl, especially fluoro or cyano.

Detailed values of Z include cyanophenyl, (cyano)(fluoro)phenyl, (chloro)(cyano)phenyl, nitrophenyl, methoxyphenyl, methanesulphonyl-

phenyl, pyridinyl, fluoro-pyridinyl, difluoro-pyridinyl, (amino)(chloro)pyridinyl, cyano-pyridinyl, methyl-pyridinyl, hydroxy-pyridinyl, methoxy-pyridinyl, oxy-pyridinyl, aminocarbonyl-pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, cyano-thienyl, aminocarbonyl-thienyl, formyl-thienyl, methoxycarbonyl-thienyl, thienyl-CH=NOH, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl and methyl-tetrazolyl.

Specific values of Z include hydrogen, fluoro, bromo, cyano, cyanomethyl, trifluoromethyl, nitro, hydroxy, methoxy, isopropoxy, formyl, methoxycarbonyl, (cyano)(fluoro)phenyl, pyridinyl, fluoro-pyridinyl, difluoro-pyridinyl, triazolyl, (methyl)(trifluoromethyl)pyrazolyl-methoxy, methyltriazolyl-methoxy and pyridinyl-methoxy.

Typically, R^1 represents hydrocarbon, a heterocyclic group, $-OR^a$, $-NR^aR^b$ or $-CO_2R^a$.

Typical values of R^a include C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl and aryl(C_{1-6})alkyl (optionally substituted by C_{1-6} alkoxy). Suitably, R^a represents methyl, ethyl, *n*-propyl, isopropyl, allyl, cyclopropyl, cyclohexyl, benzyl or methoxybenzyl.

Typical values of R^b include hydrogen and C_{1-6} alkyl. Suitably, R^b represents hydrogen or methyl, especially hydrogen.

Suitable values of R^1 include phenyl, halophenyl, dihalophenyl, C_{1-6} alkoxyphenyl, cyanophenyl, (cyano)(halo)phenyl, C_{3-7} heterocycloalkenyl, heteroaryl (optionally substituted by halo), C_{1-6} alkoxy, C_{2-6} alkenyloxy, aryl(C_{1-6})alkoxy, C_{1-6} alkylamino, C_{2-6} alkenylamino, C_{3-7} cycloalkylamino, aryl(C_{1-6})alkylamino (optionally substituted by C_{1-6} alkoxy) and C_{2-6} alkoxycarbonyl.

Individual values of R^1 include phenyl, fluorophenyl, chlorophenyl, difluorophenyl, methoxyphenyl, cyanophenyl, (cyano)(fluoro)phenyl, dihydropyrrolyl, pyridinyl, fluoro-pyridinyl, pyrazinyl, furyl, thienyl, thiazolyl, triazolyl, methoxy, ethoxy, allyloxy, benzyloxy, methylamino,

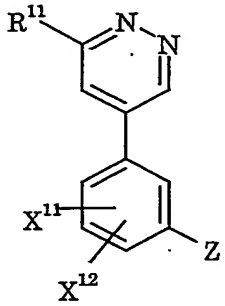
ethylamino, propylamino, isopropylamino, allylamino, cyclopropylamino, cyclohexylamino, benzylamino, methoxybenzyl-amino and ethoxycarbonyl.

In one embodiment, R^1 represents fluorophenyl (especially 2-fluorophenyl).

In another embodiment, R^1 represents fluoro-pyridinyl (especially 3-fluoropyridin-2-yl).

Suitably, R^2 represents hydrogen, methoxycarbonyl or ethoxycarbonyl. In a particular embodiment, R^2 represents hydrogen.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and *N*-oxides thereof and pharmaceutically acceptable salts thereof:



(IIA)

wherein

Z is as defined above;

X^{11} represents hydrogen, fluoro, chloro, methyl, trifluoromethyl or methoxy;

X^{12} represents hydrogen or fluoro; and

R^{11} represents phenyl, halophenyl, dihalophenyl, C_{1-6} alkoxyphenyl, cyanophenyl, (cyano)(halo)phenyl, C_{3-7} heterocycloalkenyl, heteroaryl (optionally substituted by halo), C_{1-6} alkoxy, C_{2-6} alkenyloxy, aryl(C_{1-6})alkoxy, C_{1-6} alkylamino, C_{2-6} alkenylamino, C_{3-7} cycloalkylamino, aryl(C_{1-6})alkylamino (optionally substituted by C_{1-6} alkoxy) or C_{2-6} alkoxycarbonyl.

Suitable values of X^{11} include hydrogen and fluoro, especially fluoro.

In a favoured embodiment, X^{12} represents hydrogen. In another embodiment, X^{12} represents fluoro.

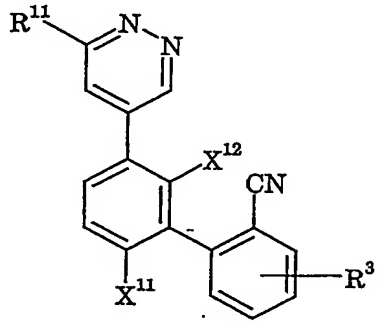
Where R^{11} represents heteroaryl, this group is suitably pyridinyl, pyrazinyl, furyl, thienyl, thiazolyl or triazolyl.

Individual values of R^{11} include phenyl, fluorophenyl, chlorophenyl, difluorophenyl, methoxyphenyl, cyanophenyl, (cyano)(fluoro)phenyl, dihydropyrrolyl, pyridinyl, fluoro-pyridinyl, pyrazinyl, furyl, thienyl, thiazolyl, triazolyl, methoxy, ethoxy, allyloxy, benzyloxy, methylamino, ethylamino, propylamino, isopropylamino, allylamino, cyclopropylamino, cyclohexylamino, benzylamino, methoxybenzyl-amino and ethoxycarbonyl.

In one embodiment, R^{11} represents fluorophenyl (especially 2-fluorophenyl).

In another embodiment, R^{11} represents fluoro-pyridinyl (especially 3-fluoropyridin-2-yl).

One representative subset of the compounds of formula IIA above is represented by the compounds of formula IIB, and *N*-oxides thereof and pharmaceutically acceptable salts thereof:



(IIB)

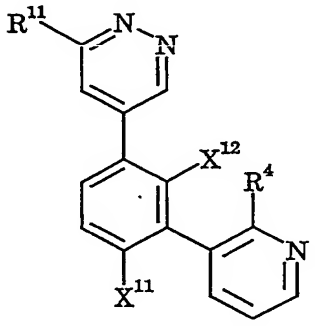
wherein X^{11}, X^{12} and R^{11} are as defined above; and

R^3 represents hydrogen or fluoro.

In one embodiment, R^3 is hydrogen.

In another embodiment, R^3 is fluoro, in which case the fluorine atom R^3 is favourably attached to the phenyl ring at the 4-, 5- or 6-position (relative to the cyano group at position 2).

Another representative subset of the compounds of formula IIA above is represented by the compounds of formula IIC, and *N*-oxides thereof and pharmaceutically acceptable salts thereof:



(IIC)

wherein X^{11}, X^{12} and R^{11} are as defined above; and

R^4 represents hydrogen, fluoro, cyano or methyl.

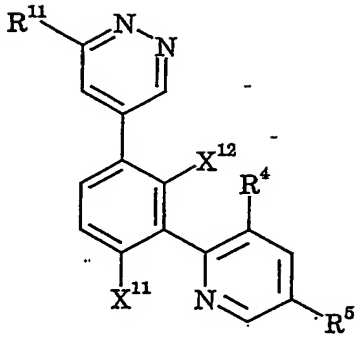
In one embodiment, R^4 is hydrogen.

In an additional embodiment, R^4 is fluoro.

In another embodiment, R^4 is cyano.

In a further embodiment, R^4 is methyl.

A further representative subset of the compounds of formula IIA above is represented by the compounds of formula IID, and *N*-oxides thereof and pharmaceutically acceptable salts thereof:



(IID)

wherein X^{11}, X^{12}, R^4 and R^{11} are as defined above; and

R^5 represents hydrogen or fluoro.

Suitably, R^5 represents hydrogen.

In another embodiment, R^5 represents fluoro.

Specific compounds within the scope of the present invention include:

3,5-diphenylpyridazine-4-carboxylic acid ethyl ester;

3,5-diphenylpyridazine-4-carboxylic acid methyl ester;

3,5-diphenylpyridazine;

5-[2-fluoro-3-(pyridin-3-yl)phenyl]3-phenylpyridazine;

5-(3-isopropoxyphenyl)-3-phenylpyridazine;

3-(6-phenylpyridazin-4-yl)benzaldehyde;

4,2′-difluoro-5′-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;

5-(3-cyanophenyl)-3-phenylpyridazine;

5-(3-bromophenyl)-3-phenylpyridazine;

3-phenyl-5-[3-(pyridin-3-yl)phenyl]pyridazine;

3-phenyl-5-(3-[1,2,4]triazol-4-ylphenyl)pyridazine;

5-[2,4-difluoro-3-(pyridin-4-yl)phenyl]-3-phenylpyridazine;

5-[3-(2-methyl-2*H*-[1,2,4]triazol-3-ylmethoxy)phenyl]-3-phenylpyridazine;

6,2′-difluoro-5′-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;

5-[4-fluoro-3-(pyridin-4-yl)phenyl]-3-phenylpyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-phenylpyridazine;

3-phenyl-5-[3-(pyridin-2-ylmethoxy)phenyl]pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-4-yl)phenyl]-3-phenylpyridazine;

5-[2-fluoro-3-(pyridin-4-yl)phenyl]-3-phenylpyridazine;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-phenylpyridazine;

5-[4-fluoro-3-(pyridin-3-yl)phenyl]-3-phenylpyridazine;

[3-(6-phenylpyridazin-4-yl)phenyl]acetonitrile;

2-fluoro-5-(6-phenylpyridazin-4-yl)benzonitrile;

5-(3-nitrophenyl)-3-phenylpyridazine;

3-(6-phenylpyridazin-4-yl)benzoic acid methyl ester;

3-(6-phenylpyridazin-4-yl)benzaldehyde;

5-(3-fluorophenyl)-3-phenylpyridazine;

3-phenyl-5-(3-trifluoromethylphenyl)pyridazine;

5-(3-methoxyphenyl)-3-phenylpyridazine;

5,2′-difluoro-5′-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;

3,2′-difluoro-5′-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;

5-(4-fluoro-3-methoxyphenyl)-3-phenylpyridazine;

6,2′-difluoro-5′-[6-(4-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;

4-fluoro-3′-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;

6,2′-difluoro-5′-[6-(thien-2-yl)pyridazin-4-yl]biphenyl-2-carbonitrile;

6,2′-difluoro-5′-[6-(4-methoxyphenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;

5′-[6-(3-chlorophenyl)pyridazin-4-yl]-6,2′-difluorobiphenyl-2-carbonitrile;

6,2′-difluoro-5′-[6-(pyridin-3-yl)pyridazin-4-yl]biphenyl-2-carbonitrile;

5′-[6-(4-chlorophenyl)pyridazin-4-yl]-6,2′-difluorobiphenyl-2-carbonitrile;

6,2′-difluoro-5′-[6-(pyridin-4-yl)pyridazin-4-yl]biphenyl-2-carbonitrile;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(4-fluorophenyl)-pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(2-fluorophenyl)pyridazine;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)-pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-3-yl)pyridazine;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-fluorophenyl)-pyridazine;

3-(2,4-difluorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-pyridazine;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-methoxyphenyl)-pyridazine;

6,2′-difluoro-5′-[6-(2-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;

6,2′-difluoro-5′-[6-(3-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;

3-[6-(3-fluorophenyl)pyridazin-4-yl]benzonitrile;

3-[6-(2-fluorophenyl)pyridazin-4-yl]benzonitrile;

3-[6-(4-fluorophenyl)pyridazin-4-yl]benzonitrile;

3-[6-(4-methoxyphenyl)pyridazin-4-yl]benzonitrile;

3-[6-(3,4-difluorophenyl)pyridazin-4-yl]benzonitrile;

3-[6-(2,4-difluorophenyl)pyridazin-4-yl]benzonitrile;

5′-[6-(2-chlorophenyl)pyridazin-4-yl]-6,2′-difluorobiphenyl-2-carbonitrile;

3-(4-methoxyphenyl)-5-phenylpyridazine;

4-fluoro-3′-[6-(4-methoxyphenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(4-methoxyphenyl)-pyridazine;

3-(4-chlorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-pyridazine;

2-{5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazin-3-yl}-5-fluorobenzonitrile;

3-(4-chlorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(furan-3-yl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(furan-2-yl)pyridazine;

3-(2,3-difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(thien-3-yl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(thien-2-yl)pyridazine;

3-(2,5-difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-pyridazine;

3-(3,4-difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-pyridazine;

4-{5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazin-3-yl}benzonitrile;

N-[5-(3-bromophenyl)pyridazin-3-yl]-*N*-methylamine;

N-[5-(3-bromophenyl)pyridazin-3-yl]-*N*-isopropylamine;

N-[5-(3-bromophenyl)pyridazin-3-yl]-*N*-cyclopropylamine;

N-allyl-*N*-[5-(3-bromophenyl)pyridazin-3-yl]amine;

N-[5-(3-bromophenyl)pyridazin-3-yl]-*N*-ethylamine

N-benzyl-*N*-[5-(3-bromophenyl)pyridazin-3-yl]amine;

N-[5-(3-bromophenyl)pyridazin-3-yl]-*N*-(2-methoxybenzyl)amine;

5-(3-bromophenyl)-3-(2,5-dihydropyrrol-1-yl)pyridazine;

5-(3-bromophenyl)-3-ethoxypyridazine;

3-allyloxy-5-(3-bromophenyl)pyridazine;

3-(6-isopropylaminopyridazin-4-yl)benzonitrile;

3-(6-benzylaminopyridazin-4-yl)benzonitrile;

3-[6-(2-methoxybenzylamino)pyridazin-4-yl]benzonitrile;

3-(6-benzyloxypyridazin-4-yl)benzonitrile;

3′-(6-ethylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;

4-fluoro-3′-(6-isopropylaminopyridazin-4-yl)biphenyl-2-carbonitrile;

4-fluoro-3′-(6-propylaminopyridazin-4-yl)biphenyl-2-carbonitrile;

3′-(6-cyclopropylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;

3′-(6-allylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;

3′-(6-benzylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;

4-fluoro-3′-(6-methylaminopyridazin-4-yl)biphenyl-2-carbonitrile;

4-fluoro-3′-(6-methoxypyridazin-4-yl)biphenyl-2-carbonitrile;

3′-(6-ethoxypyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;

3′-(6-benzyloxypyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;

5-(4-fluoro-3-hydroxyphenyl)-3-phenylpyridazine;

5-[4-fluoro-3-(2-methyl-2*H*-[1,2,4]triazol-3-ylmethoxy)phenyl]-3-phenylpyridazine;

5-[4-fluoro-3-(1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-ylmethoxy)phenyl]-3-phenylpyridazine;

5-[4-fluoro-3-(pyridin-4-ylmethoxy)phenyl]-3-phenylpyridazine;

5-[4-fluoro-3-(pyridin-3-ylmethoxy)phenyl]-3-phenylpyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-4-yl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyrazin-2-yl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(thiazol-2-yl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-2-yl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoropyridin-2-yl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(1*H*-[1,2,3]triazol-4-yl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine-3-carboxylic acid ethyl ester;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)-pyridazine-1-oxide;

3-(2,6-difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-pyridazine;

and pharmaceutically acceptable salts thereof.

Also provided by the present invention is a method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

Further provided by the present invention is a method for the treatment and/or prevention of convulsions (e.g. in a patient suffering from epilepsy or a related disorder) which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

The binding affinity (K_i) of the compounds according to the present invention for the α3 subunit of the human $GABA_A$ receptor is conveniently as measured in the assay described hereinbelow: The α3 subunit binding affinity (K_i) of the anxiolytic compounds of the invention is ideally 50 nM or less, preferably 10 nM or less, and more preferably 5 nM or less.

The anxiolytic compounds according to the present invention will ideally elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor. Moreover, the compounds of the invention will ideally elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

The potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α3 and α1 subunits of the human $GABA_A$ receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, **50**, 670-678. The procedure will suitably be carried out utilising cultures of stably transfected eukaryotic cells, typically of stably transfected mouse Ltk- fibroblast cells.

The compounds according to the present invention may exhibit anxiolytic activity, as may be demonstrated by a positive response in the elevated plus maze and conditioned suppression of drinking tests (cf. Dawson *et al.*, *Psychopharmacology*, 1995, **121**, 109-117). Moreover, the compounds of the invention are likely to be substantially non-sedating, as may be confirmed by an appropriate result obtained from the response sensitivity (chain-pulling) test (cf. Bayley *et al.*, *J. Psychopharmacol.*, 1996, **10**, 206-213).

The compounds according to the present invention may also exhibit anticonvulsant activity. This can be demonstrated by the ability to block

pentylenetetrazole-induced seizures in rats and mice, following a protocol analogous to that described by Bristow *et al.* in *J. Pharmacol. Exp. Ther.*, 1996, **279**, 492-501.

In another aspect, the present invention provides a method for the treatment and/or prevention of cognitive disorders, including dementing conditions such as Alzheimer's disease, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

Cognition enhancement can be shown by testing the compounds in the Morris watermaze as reported by McNamara and Skelton, *Psychobiology*, 1993, **21**, 101-108. Further details of relevant methodology are described in WO 96/25948.

Cognitive disorders for which the compounds of the present invention may be of benefit include delirium, dementia, amnestic disorders, and cognition deficits, including age-related memory deficits, due to traumatic injury, stroke, Parkinson's disease and Down Syndrome. Any of these conditions may be attributable to substance abuse or withdrawal. Examples of dementia include dementia of the Alzheimer's type with early or late onset, and vascular dementia, any of which may be uncomplicated or accompanied by delirium, delusions or depressed mood; and dementia due to HIV disease, head trauma, Parkinson's disease or Creutzfeld-Jakob disease.

In order to elicit their behavioural effects, the compounds of the invention will ideally be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably, the compounds of the invention will be capable of exerting their beneficial therapeutic action following administration by the oral route.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules,

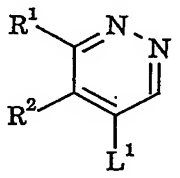
sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection

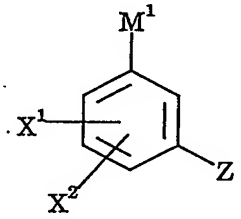
include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of neurological disorders, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds in accordance with the present invention may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:



(III)



(IV)

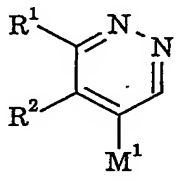
wherein X^1, X^2, Z, R^1 and R^2 are as defined above, L^1 represents a suitable leaving group, and M^1 represents a boronic acid moiety $-B(OH)_2$ or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol, or M^1 represents $-Sn(Alk)_3$ in which Alk represents a C_{1-6} alkyl group, typically *n*-butyl; in the presence of a transition metal catalyst.

The leaving group L^1 is typically a halogen atom, e.g. iodo or bromo.

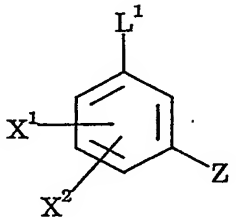
The transition metal catalyst of use in the reaction between compounds III and IV is suitably tetrakis(triphenylphosphine)-palladium(0). The reaction is conveniently carried out at an elevated

temperature in a solvent such as *N,N*-dimethylacetamide, 1,4-dioxane or tetrahydrofuran, advantageously in the presence of potassium phosphate, copper(I) iodide, sodium carbonate or cesium carbonate. Alternatively, the transition metal catalyst employed may be dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II), in which case the reaction is conveniently effected at an elevated temperature in a solvent such as *N,N*-dimethylformamide, advantageously in the presence of potassium phosphate.

In an alternative procedure, the compounds according to the present invention may be prepared by a process which comprises reacting a compound of formula V with a compound of formula VI:



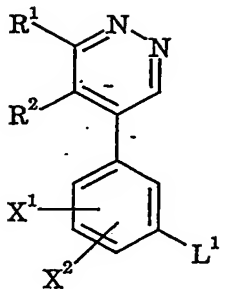
(V)



(VI)

wherein X^1, X^2, Z, R^1, R^2, L^1 and M^1 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

In another procedure, the compounds according to the present invention may be prepared by a process which comprises reacting a compound of formula VII with a compound of formula VIII:



(VII)

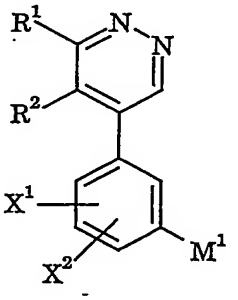
M^1—Z

(VIII)

wherein X^1, X^2, Z, R^1, R^2, L^1 and M^1 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

In the compounds of formula VI and VII above, the leaving group L^1 is typically trifluoromethanesulfonyloxy (triflyloxy); or a halogen atom, e.g. bromo.

Alternatively, the compounds according to the present invention may be prepared by a process which comprises reacting a compound of formula IX with a compound of formula X:



(IX)

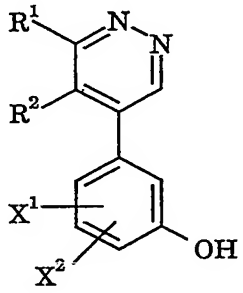
L^1—Z

(X)

wherein X^1, X^2, Z, R^1, R^2, L^1 and M^1 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

In an additional procedure, the compounds according to the present invention in which Z represents C_{1-6} alkoxy or optionally substituted

heteroaryl(C_{1-6})alkoxy may be prepared by a process which comprises reacting a compound of formula XI with a compound of formula XII:



(XI)

Z^1 — OH

(XII)

wherein X^1, X^2, R^1 and R^2 are as defined above, and Z^1 represents C_{1-6} alkyl or optioanlly substituted heteroaryl(C_{1-6})alkyl; in the presence of triphenylphosphine and a dialkyl azodicarboxylate, e.g. diisopropyl azodicarboxylate (DIAD) or diethyl azodicarboxylate (DEAD).

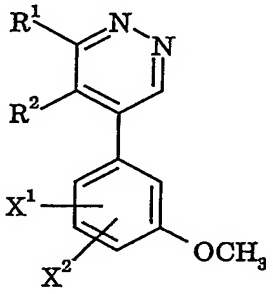
The reaction is conveniently carried out by stirring in a solvent such as tetrahydrofuran.

Where M^1 in the intermediates of formula IV and IX above represents a boronic acid moiety -$B(OH)_2$ or a cyclic ester thereof formed with pinacol or neopentyl glycol, the relevant compound IV or IX may be prepared by reacting bis(pinacolato)diboron or bis(neopentyl glycolato)diborane respectively with a compound of formula VI or VII as defined above; in the presence of a transition metal catalyst.

The transition metal catalyst of use in the reaction between bis(pinacolato)diboron or bis(neopentyl glycolato)diborane and compound VI or VII is suitably dichloro[1,1′-bis(diphenylphosphino)ferrocene]-palladium(II). The reaction is conveniently carried out at an elevated temperature in a solvent such as 1,4-dioxane, optionally in admixture with dimethylsulfoxide, typically in the presence of 1,1′-bis(diphenylphosphino)ferrocene and/or potassium acetate.

Where L^1 in the intermediates of formula VII above represents triflyloxy, the relevant compound VII may be prepared by reacting the appropriate compound of formula XI as defined above with triflic anhydride, typically in the presence of pyridine. Analogous conditions may be utilised for preparing a compound of formula VI wherein L^1 represents triflyloxy from the corresponding hydroxy precursor.

The intermediates of formula XI above may suitably be prepared from the appropriate methoxy-substituted precursor of formula XIII:



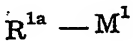
(XIII)

wherein X^1, X^2, R^1 and R^2 are as defined above; by treatment with boron tribromide, typically in chloroform or dichloromethane; or with hydrogen bromide, typically in acetic acid at reflux.

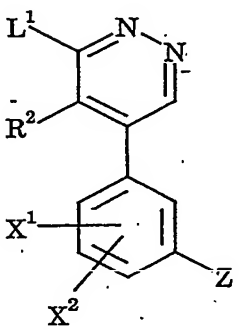
Where M^1 in the intermediates of formula V above represents $-Sn(Alk)_3$ and Alk is as defined above, this compound may be prepared by reacting a compound of formula III as defined above with a reagent of formula $(Alk)_3Sn\text{-}Hal$, in which Hal represents a halogen atom, typically chloro. The reaction is conveniently effected by treating compound III with isopropylmagnesium chloride, typically in a solvent such as tetrahydrofuran, with subsequent addition of the stannyl reagent $(Alk)_3Sn\text{-}Hal$.

In a further procedure, the compounds according to the present invention wherein R^1 represents an aryl or heteroaryl moiety may be

prepared by a process which comprises reacting a compound of formula XIV with a compound of formula XV:



(XIV)



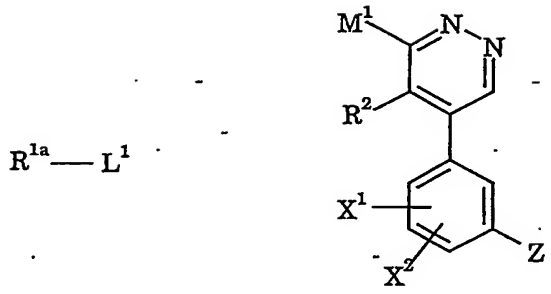
(XV)

wherein X^1, X^2, Z, R^2, L^1 and M^1 are as defined above, and R^{1a} represents an aryl or heteroaryl moiety; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

In the compounds of formula XV above, the leaving group L^1 is typically triflyloxy; or a halogen atom, e.g. chloro.

The transition metal catalyst of use in the reaction between compounds XIV and XV is suitably tetrakis(triphenylphosphine)-palladium(0), in which case the reaction is conveniently effected at an elevated temperature in a solvent such as tetrahydrofuran or 1,4-dioxane, typically in the presence of sodium carbonate. Alternatively, the transition metal catalyst may suitably be palladium bis(diphenylphosphinylbutane)dichloride, in which case the reaction is conveniently effected at an elevated temperature in a solvent such as tetrahydrofuran, typically in the presence of sodium carbonate.

In a still further procedure, the compounds according to the present invention wherein R^1 represents an aryl or heteroaryl moiety may be prepared by a process which comprises reacting a compound of formula XVI with a compound of formula XVII:

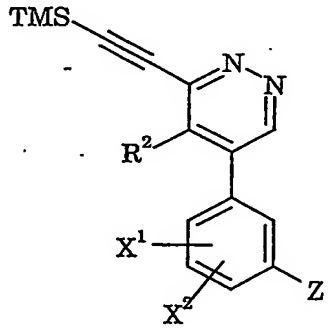


(XVI) (XVII)

wherein X^1, X^2, Z, R^{1a}, R^2, L^1 and M^1 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

The intermediates of formula XVII wherein M^1 represents -Sn(Alk)$_3$ and Alk represents C_{1-6} alkyl, e.g. methyl, may be prepared by reacting a compound of formula XV as defined above with a reagent of formula (Alk)$_3$Sn-Sn(Alk)$_3$. The reaction is conveniently effected in the presence of a transition metal catalyst, e.g. tetrakis(triphenylphosphine)palladium(0), with heating in a solvent such as 1,4-dioxane, typically in the presence of lithium chloride.

In a yet further procedure, the compounds according to the present invention wherein R^1 represents 1*H*-[1,2,3]triazol-4-yl may be prepared by a process which comprises reacting a compound of formula XVIII:



(XVIII)

wherein X^1, X^2, Z and R^2 are as defined above, and TMS is an abbreviation for trimethylsilanyl; with sodium azide.

The reaction is conveniently effected by stirring the reactants in a solvent such as *N,N*-dimethylformamide.

The intermediates of formula XVIII may be prepared by reacting a compound of formula XV with TMS-acetylene, in the presence of a transition metal catalyst such as bis(triphenylphosphine)palladium(II) chloride. The reaction is conveniently effected by stirring in a solvent such as tetrahydrofuran, typically in the presence of triethylamine, triphenylphosphine and copper(I) chloride.

The compounds according to the present invention wherein R^1 represents $-OR^a$ may be prepared by a process which comprises reacting a compound of formula XV as defined above with a compound of formula R^a-OH, wherein R^a is as defined above. The reaction is conveniently carried out in the presence of a base such as sodium hydride or sodium ethoxide.

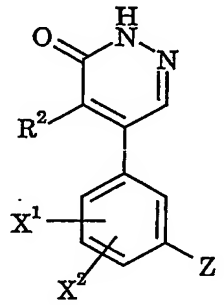
The compounds according to the present invention wherein R^1 represents $-NR^aR^b$ may be prepared by a process which comprises reacting a compound of formula XV as defined above with a compound of formula H-NR^aR^b, wherein R^a and R^b are as defined above. The reaction is conveniently effected by stirring at an elevated temperature, typically in a solvent such as tetrahydrofuran.

The compounds according to the present invention wherein R^1 represents $-CO_2R^a$ may be prepared by a process which comprises reacting a compound of formula XV as defined above with carbon dioxide and a compound of formula R^a-OH, wherein R^a is as defined above; in the presence of a transition metal catalyst.

The transition metal catalyst of use in the foregoing reaction is ideally [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) chloride, in which case the reaction is conveniently carried out at an elevated temperature in a solvent such as *N,N*-dimethylformamide, optionally in

admixture with dichloromethane, typically in the presence of sodium acetate.

The intermediates of formula XV wherein L^1 represents triflyloxy may be prepared by reacting a compound of formula XIX:

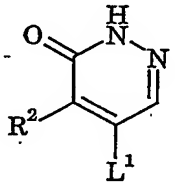


(XIX)

wherein X^1, X^2, Z and R^2 are as defined above; with *N*-phenyltriflylimide, typically in the presence of triethylamine, in a solvent such as dichloromethane.

Moreover, the intermediates of formula XV wherein L^1 represents chloro may be prepared by treating the requisite compound of formula XIX with phosphorus oxychloride at an elevated temperature.

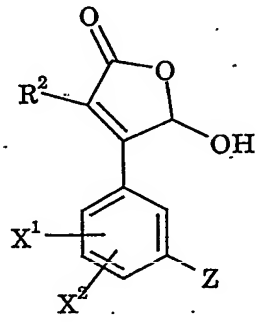
The intermediates of formula XIX may be prepared by reacting a compound of formula IV as defined above with a compound of formula XX:



(XX)

wherein R^2 and L^1 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

Alternatively, the intermediates of formula XIX may be prepared by reacting a compound of formula XXI:



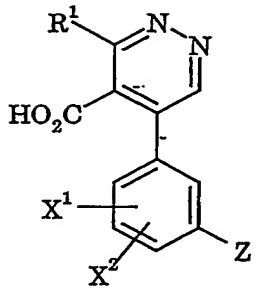
(XXI)

wherein X^1, X^2, Z and R^2 are as defined above; with hydrazine hydrate, typically in ethanol at reflux.

The compounds according to the present invention wherein Z represents cyano may be prepared by a process which comprises reacting a compound of formula VII above wherein L^1 represents a halogen atom, e.g. bromo, with zinc cyanide; in the presence of a transition metal catalyst.

The transition metal catalyst of use in the foregoing reaction is ideally tetrakis(triphenylphosphine)palladium(0), in which case the reaction is conveniently effected at an elevated temperature in a solvent such as *N,N*-dimethylformamide.

The compounds according to the present invention wherein R^2 represents methoxycarbonyl may be prepared by a process which comprises reacting a compound of formula XXII:



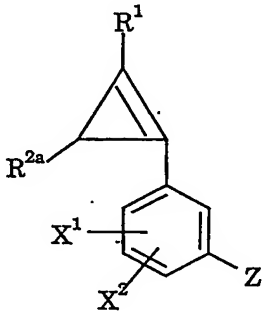
(XXII)

wherein X^1, X^2, Z and R^1 are as defined above; with diazomethane.

The reaction is conveniently accomplished by stirring in a solvent such as diethyl ether.

The intermediates of formula XXII may be prepared by saponifying a compound of formula I wherein R^2 represents C_{2-6} alkoxycarbonyl, typically by treatment with potassium hydroxide in refluxing aqueous methanol.

The compounds according to the present invention wherein R^2 represents C_{2-6} alkoxycarbonyl may be prepared by a process which comprises reacting a compound of formula XXIII:



(XXIII)

wherein X^1, X^2, Z and R^1 are as defined above, and R^{2a} represents C_{2-6} alkoxycarbonyl; with diazomethane.

The reaction is conveniently effected by stirring in a solvent such as diethyl ether.

The compounds of formula XI and XIII above correspond to compounds of formula I as defined above wherein Z represents hydroxy and methoxy respectively, and they may therefore be prepared by any of the methods described above for the preparation of the compounds according to the invention. Moreover, where L^1 in compounds VII and XV above represents a halogen atom, these compounds correspond to compounds of formula I as defined above, and they therefore constitute compounds in accordance with the invention in their own right.

Where they are not commercially available, the starting materials of formula III, VIII, X, XII, XIV, XVI, XX, XXI and XXIII may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I initially obtained may be converted into the *N*-oxide derivative thereof by treatment with *m*-chloroperbenzoic acid. A compound of formula I wherein R^1 represents $-C(O\text{-}Alk^1)_2R^a$ initially obtained, wherein Alk^1 is C_{1-6} alkyl, typically methyl or ethyl, may be converted into the corresponding compound of formula I wherein R^1 represents $-COR^a$ by hydrolysis with a mineral acid, typically aqueous hydrochloric acid. A compound wherein R^1 represents formyl may be reduced with sodium triacetoxyborohydride to the corresponding compound wherein R^1 represents hydroxymethyl. A compound of formula I wherein R^1 represents C_{2-6} alkoxycarbonyl may be reduced with lithium aluminium hydride to the corresponding compound of formula I wherein R^1 represents hydroxymethyl. A compound of formula I wherein R^1 represents hydroxymethyl may be oxidised to the corresponding compound of formula I wherein R^1 represents formyl by treatment with manganese dioxide. The formyl derivative thereby obtained may be condensed with a

hydroxylamine derivative of formula H_2N-OR^b to provide a compound of formula I wherein R^1 represents -CH=NOR^b. Furthermore, a compound of formula I wherein R^1 represents -CH=NOH may be treated with triethylamine in the presence of 1,1′-carbonyldiimidazole to afford a corresponding compound of formula I wherein R^1 represents cyano. Alternatively, the compound of formula I wherein R^1 represents formyl may be reacted with a Grignard reagent of formula R^aMgBr to afford a compound of formula I wherein R^1 represents -CH(OH)R^a, and this compound may in turn be oxidised using manganese dioxide to the corresponding compound of formula I wherein R^1 represents -COR^a. The latter compound may then be condensed with a hydroxylamine derivative of formula H_2N-OR^b to provide a compound of formula I wherein R^1 represents -CR^a=NOR^b. A compound of formula I wherein R^1 represents -CH(OH)R^a may be converted into the corresponding compound of formula I wherein R^1 represents -$CHFR^a$ by treatment with (diethylamino)sulfur trifluoride (DAST). Similarly, a compound of formula I wherein R^1 represents -COR^a may be converted into the corresponding compound of formula I wherein R^1 represents -CF_2R^a by treatment with DAST. A compound of formula I wherein R^1 represents amino may be converted into the corresponding compound of formula I wherein R^1 represents chloro by diazotisation, using sodium nitrite, followed by treatment with copper(I) chloride. A compound of formula I wherein R^1 represents -$COCH_3$ may be treated with thioacetamide in the presence of pyridinium tribromide to furnish the corresponding compound of formula I wherein R^1 represents 2-methylthiazol-5-yl. Moreover, a compound of formula I wherein R^1 is formyl may be treated with (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) in the presence of potassium carbonate to afford the corresponding compound of formula I wherein R^1 represents oxazol-5-yl. A compound of formula I wherein R^1 represents hydroxymethyl may be treated with carbon tetrabromide and triphenylphosphine to afford the corresponding compound of formula I wherein R^1 represents bromomethyl, which may

then be reacted (typically *in situ*) with the sodium salt of imidazole or 1*H*-[1,2,4]triazole to provide a compound of formula I wherein R^1 represents imidazol-1-ylmethyl or [1,2,4]triazol-1-ylmethyl respectively; or with the sodium salt of 1*H*-[1,2,3]triazole to provide a mixture of compounds of formula I wherein R^1 represents [1,2,3]triazol-1-ylmethyl and [1,2,3]triazol-2-ylmethyl; or with morpholine to provide a compound of formula I wherein R^1 represents morpholin-4-ylmethyl. A compound of formula I wherein Z is substituted with methoxy may be converted to the corresponding compound wherein Z is substituted with hydroxy by treatment with boron tribromide.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potently inhibit the binding of [^{3}H]-flumazenil to the benzodiazepine binding site of human $GABA_A$ receptors containing the α2 and/or α3 and/or α5 subunit stably expressed in Ltk$^-$ cells.

Reagents

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH_2PO_4, 100 mM KCl, pH 7.4 at room temperature.
- [^{3}H]-Flumazenil (18 nM for α1β3γ2 cells; 18 nM for α2β3γ2 cells; 10 nM for α3β3γ2 cells; 10 nM for α5β3γ2 cells) in assay buffer.
- Flunitrazepam 100 μM in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

Harvesting Cells

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 µl of assay buffer.
- 50 µl of [^{3}H]-flumazenil (final concentration for $\alpha1\beta3\gamma2$: 1.8 nM; for $\alpha2\beta3\gamma2$: 1.8 nM; for $\alpha3\beta3\gamma2$: 1.0 nM; for $\alpha5\beta3\gamma2$: 1.0 nM).
- 50 µl of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 µM final concentration.
- 100 µl of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [^{3}H]-flumazenil from the $\alpha2$ and/or $\alpha3$ and/or $\alpha5$ subunit of the human $GABA_A$ receptor of 100 nM or less.

EXAMPLE 1

3,5-Diphenylpyridazine-4-carboxylic acid ethyl ester

2,3-Diphenylcycloprop-2-enecarboxylic acid ethyl ester (3.5 g, 13.2 mmol) in diethyl ether (20 ml) was added to a solution of diazomethane (66.4 mmol) in 125 ml ether and stirred in the absence of light for 3 days.

Acetic acid was added dropwise until evolution of N_2 gas had ceased. Further portions of acetic acid were added before heating to reflux for 4 h. The reaction was concentrated and purified by column chromatography using 10-30% ethyl acetate/hexanes to give the *title compound* as a pale yellow solid (1.77 g). δ_H (400 MHz, d^6 DMSO) 0.84 (3H, t, *J* 7.0), 4.02 (2H, q, *J* 7.0), 7.54-7.58 (8H, m), 7.62-7.65 (2H, m), 9.48 (1H, s); *m/z* (ES^+) 305.

EXAMPLE 2

3,5-Diphenylpyridazine-4-carboxylic acid methyl ester

The product from Example 1 (1.17 g, 3.84 mmol) and potassium hydroxide (0.86 g, 15.3 mmol) were heated to reflux in methanol/H_2O (25 ml/3 ml) for 18 h. The reaction was cooled to room temperature and acidified with 2N HCl to give 3,5-diphenylpyridazine-4-carboxylic acid as a pale yellow solid which was collected by filtration (0.94 g). δ_H (400 MHz, d^6 DMSO) 7.55-7.57 (6H, m), 7.60-7.63 (2H, m), 7.71-7.73 (2H, m), 9.40 (1H, s); *m/z* (ES^+) 277.

A solution of diazomethane (0.6 mmol) in diethyl ether (5 ml) was added dropwise to the product from above (0.1 g, 0.36 mmol) suspended in diethyl ether (10 ml). The resultant clear solution was stirred for 18 h. Acetic acid was added and the reaction stirred for 1 h before concentrating. The *title compound* was obtained as a pale yellow solid by recrystallising from ethyl acetate-hexanes (78 mg). δ_H (400 MHz, d^6 DMSO) 3.54 (3H, s), 7.53-7.58 (8H, m), 7.62-7.66 (2H, m), 9.49 (1H, s); *m/z* (ES^+) 291.

EXAMPLE 3

3,5-Diphenylpyridazine

3-Phenyl-5-(tri-*n*-butylstannyl)pyridazine (100 mg, 0.22 mmol), bromobenzene (32 µl, 0.27 mmol) and tetrakis(triphenylphosphine)-palladium(0) (5 mg) in tetrahydrofuran (2 ml) were combined and heated

to 150°C for 600 s in a Smith Synthesiser microwave reactor (Personal Chemistry, Uppsala, Sweden). The reaction was diluted with CH_2Cl_2 (6 ml) and H_2O (2 ml) then poured into a PTFE (5 μM) fritted syringe barrel. The organic phase was collected and concentrated to leave 100 mg of crude product. Part of the sample was purified by HPLC with mass triggered fraction collection to give the *title compound* as a gum (3.1 mg). δ_H (400 MHz, d^6 DMSO) 7.55-7.64 (6H, m), 8.06 (2H, dd, *J* 8.0, 1.6), 8.28 (2H, dd, *J* 8.0, 1.6), 8.46-8.47 (1H, d, *J* 4.0), 9.62 (1H, d, *J* 4.0); *m/z* (ES^+) 233 (MH^+).

EXAMPLE 4

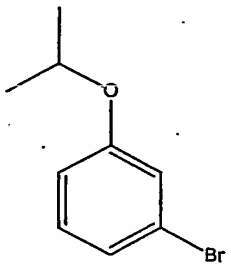
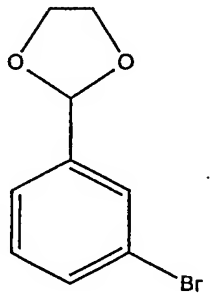
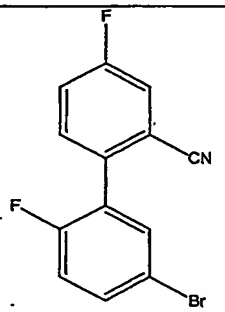
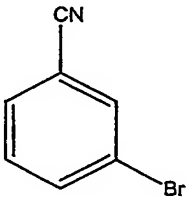
5-[2-Fluoro-3-(pyridin-3-yl)phenyl]3-phenylpyridazine

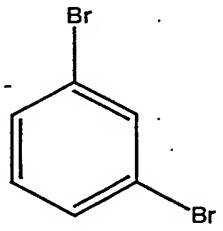
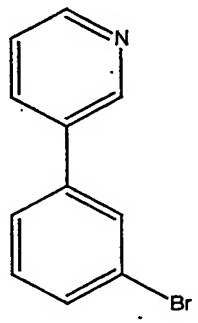
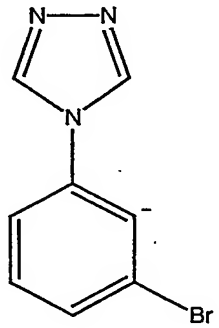
5-Iodo-3-phenylpyridazine (60 mg, 0.14 mmol), 2-fluoro-3-(pyridin-3-yl)phenylboronic acid (32 mg), tetrakis(triphenylphosphine)palladium(0) (5 mg) and 2N Na_2CO_3 (1 ml) in tetrahydrofuran (4 ml) were combined and heated to 150°C for 600 s in a Smith Synthesiser microwave reactor. The reaction was diluted with CH_2Cl_2 (6 ml) and H_2O (2 ml) then poured into a PTFE (5 μM) fritted syringe barrel. The organic phase was collected, concentrated and recrystallised from methanol-CH_2Cl_2-isopropanol to give the *title compound* as a colourless solid (36 mg). δ_H (400 MHz, d^6 DMSO) 7.55-7.66 (5H, m), 7.77-7.81 (1H, m), 7.91-7.95 (1H, m), 8.08-8.11 (1H, m), 8.25-8.27 (2H, m), 8.48 (1H, m), 8.66 (1H, dd, *J* 1.6, 4.7), 8.87 (1H, d, *J* 2.0), 9.53 (1H, t, *J* 2.2); *m/z* (ES^+) 328 (MH^+).

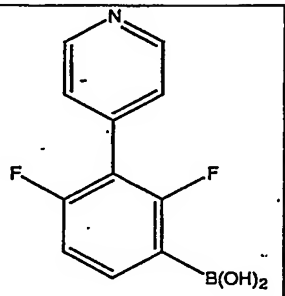
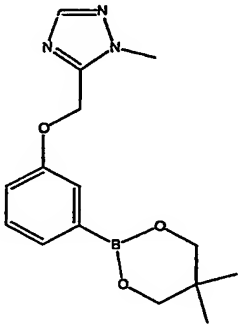
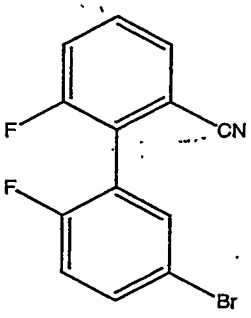
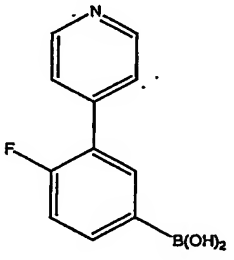
EXAMPLES 5 TO 32

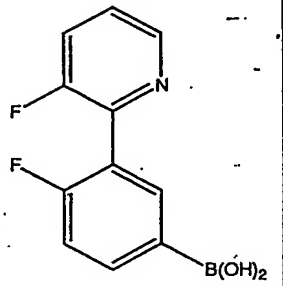
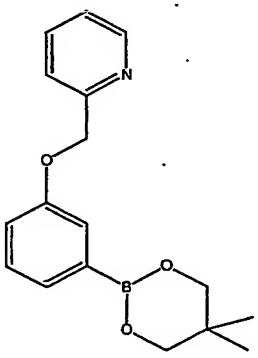
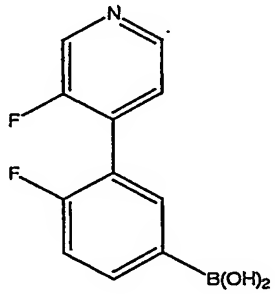
The compounds in Table 1 were prepared, using the aryl halide, boronic acid or ester starting materials shown, in an analogous manner to that described in Example 3 or 4. Samples were purified as described in Example 3 or by recrystallisation from methanol-ethyl acetate, CH_2Cl_2 or CH_2Cl_2-isopropanol.

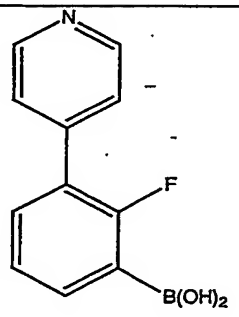
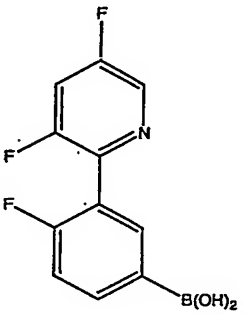
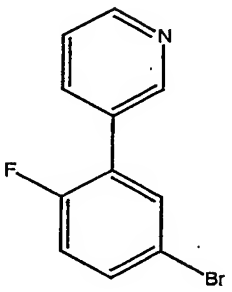
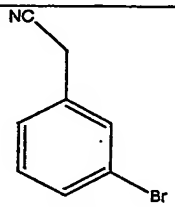
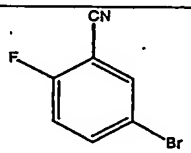
Table 1

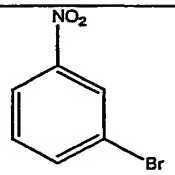
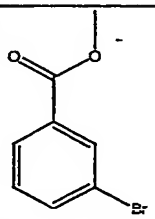
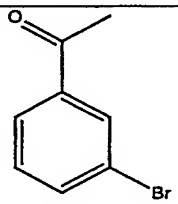
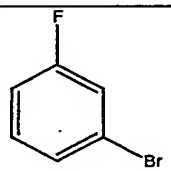
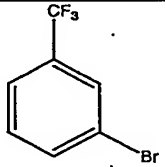
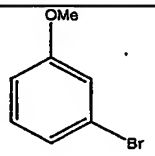
EX. NO.	STARTING MATERIAL	PRODUCT	δ_H (400 MHz, d^6 DMSO)	*m/z* (ES^+)
5		5-(3-Isopropoxy-phenyl)-3-phenyl-pyridazine	1.32 (6H, d, *J* 8), 4.80 (1H, quin, *J* 8), 7.10-7.12 (1H, m), 7.48-7.61 (7H, m), 8.26-8.28 (1H, m), 8.43 (1H, d, *J* 2), 9.58 (1H, d, *J* 2).	291
6		3-(6-Phenyl-pyridazin-4-yl)-benzaldehyde	7.56-7.69 (4H, m), 7.77 (1H, d, *J* 8), 7.84 (1H, d, *J* 8), 8.09 (1H, dd, *J* 1.2, 8), 8.23 (2H, m), 8.32 (1H, d, *J* 2), 9.29 (1H, d, *J* 2), 10.00 (1H, s).	261
7		4,2′-Difluoro-5′-(6-phenyl-pyridazin-4-yl)biphenyl-2-carbonitrile	7.56-7.67 (4H, m), 7.79-7.86 (2H, m), 8.05-8.08 (1H, m), 8.26-8.32 (4H, m), 8.55 (1H, d, *J* 4), 9.69 (1H, d, *J* 4)	370
8		5-(3-Cyanophenyl)-3-phenyl-pyridazine	7.57-7.64 (3H, m), 7.81 (1H, t, *J* 8), 8.03 (1H, d, *J* 8), 8.30-8.35 (2H, m), 8.41 (1H, d, *J* 8), 8.59 (1H, d, *J* 4),	258

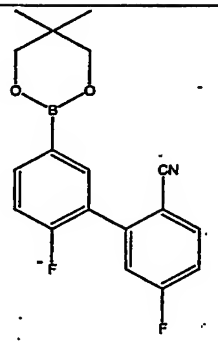
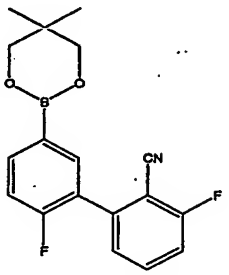
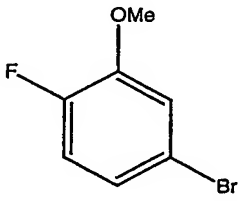
			8.63 (1H, s), 9.69 (1H, d, *J* 4).	
9		5-(3-Bromophenyl)-3-phenyl-pyridazine	7.53-7.62 (4H, m), 7.76 (1H, d, *J* 12), 8.06 (1H, d, *J* 12), 8.28-8.33 (3H, m), 8.51 (1H, d, *J* 4), 9.62 (1H, d, *J* 4).	312
10		3-Phenyl-5-[3-(pyridin-3-yl)-phenyl]-pyridazine	7.48-7.66 (4H, m), 7.73 (1H, t, *J* 7.8), 7.92-7.94 (1H, m), 8.12-8.13 (1H, m), 8.26-8.33 (3H, m), 8.41 (1H, t, *J* 1.8), 8.62-8.64 (2H, m), 9.10 (1H, dd, *J* 2.0, 0.8), 9.75 (1H, d, *J* 2.3).	310
11		3-Phenyl-5-(3-[1,2,4]triazol-4-ylphenyl)pyrid-azine	7.56-7.66 (4H, m), 7.79 (1H, t, *J* 7.8), 7.90-7.93 (1H, m), 8.14-8.16 (1H, m), 8.29-8.31 (1H, dd, *J* 0.8, 0.8), 8.42 (1H, t, *J* 2.0), 8.61 (1H, d, *J* 2.0), 9.29 (2H, s), 9.76 (1H, d, *J* 2.3).	300
12		5-[2,4-Difluoro-3-(pyridin-4-yl)-phenyl]-3-phenyl-	7.53-7.64 (6H, m), 8.04-8.10 (1H, m), 8.26 (2H, dd, *J* 1.8,	346

		pyridazine	8.0), 8.46 (1H, d, *J* 0.8), 8.77 (2H, dd, *J* 1.4, 4.5), 9.50 (1H, t, *J* 1.8).	
13		5-[3-(2-Methyl-2*H*-[1,2,4]triazol-3-ylmethoxy)-phenyl]-3-phenyl-pyridazine	3.94 (3H, s), 5.46 (2H, s), 7.25 (1H, dd, *J* 2.0, 7.6), 7.52-7.62 (4H, m), 7.70 (1H, d, *J* 8.4), 7.79-7.80 (1H, m), 7.96 (1H, s), 8.28-8.30 (2H, m), 8.48 (1H, d, *J* 4.0), 9.63 (1H, s).	344
14		6,2′-Difluoro-5′-(6-phenyl-pyridazin-4-yl)-biphenyl-2-carbonitrile	7.54-7.87 (6H, m), 7.98 (1H, dd, *J* 1.2, 7.4), 8.28-8.31 (2H, m), 8.34-8.38 (1H, m), 8.48 (1H, dd, *J* 2.5, 6.8), 8.55 (1H, d, *J* 2.0), 9.69 (1H, d, *J* 2.0).	312
15		5-[4-Fluoro-3-(pyridin-4-yl)-phenyl]-3-phenyl-pyridazine	7.54-7.68 (3H, m), 7.75-7.77 (2H, m), 8.21-8.25 (1H, m), 8.29-8.36 (3H, m), 8.60 (1H, d, *J* 2.3), 8.73-8.74 (2H, m), 9.73 (1H, d, *J* 2.3).	328

16		5-[4-Fluoro-3-(3-fluoro-pyridin-2-yl)-phenyl]-3-phenyl-pyridazine	7.53-7.68 (5H, m), 7.92-7.97 (1H, m), 8.26-8.35 (4H, m), 8.55 (1H, d, *J* 2.3), 8.63-8.65 (1H, m), 9.67 (1H, d, *J* 2.3).	346
17		3-Phenyl-5-[3-(pyridin-2-ylmethoxy)-phenyl]-pyridazine	5.33 (2H, s), 7.21-7.24 (1H, m), 7.30-7.40 (1H, m), 7.50-7.67 (6H, m), 7.76 (1H, t, *J* 2.0), 7.85-7.89 (1H, m), 8.29 (2H, d, *J* 1.6), 8.48 (1H, d, *J* 2.3), 8.60-8.65 (1H, m), 9.63 (1H, d, *J* 2.3).	340
18		5-[4-Fluoro-3-(3-fluoro-pyridin-4-yl)phenyl]-3-phenyl-pyridazine	7.54-7.68 (4H, m), 7.77 (1H, dd, *J* 5.1, 6.3), 8.29-8.36 (4H, m), 8.57 (1H, d, *J* 2.3), 8.63 (1H, dd, *J* 1.2, 5.1), 8.77 (1H, d, *J* 2.0), 9.71 (1H, d, *J* 2.3).	346
19		5-[2-Fluoro-3-(pyridin-4-yl)-phenyl]-3-phenyl-pyridazine	7.50-7.71 (6H, m), 7.79-7.83 (1H, m), 7.94-7.99 (1H, m), 8.25-8.27 (2H, m), 8.48 (1H, dd, *J* 0.8, 1.2); 8.72-8.73 (2H,	328

			m), 9.53 (1H, t, *J* 2.0).	
20		5-[3-(3,5-Difluoro-pyridin-2-yl)-4-fluorophenyl]-3-phenyl-pyridazine	7.54-7.68 (4H, m), 8.16-8.22 (1H, m), 8.27-8.33 (4H, m), 8.54 (1H, d, *J* 2.0), 8.75 (1H, d, *J* 2.3), 9.66 (1H, d, *J* 2.3).	364
21		5-[4-Fluoro-3-(pyridin-3-yl)-phenyl]-3-phenyl-pyridazine	7.54-7.64 (5H, m), 8.13-8.22 (2H, m), 8.30-8.33 (3H, m), 8.60 (1H, d, *J* 2.5), 8.68 (1H, dd, *J* 1.6, 4.7), 8.94 (1H, s), 9.73 (1H, d, *J* 2.5).	328
22		[3-(6-Phenyl-pyridazin-4-yl)phenyl]-acetonitrile		272
23		2-Fluoro-5-(6-phenyl-pyridazin-4-yl)benzonitrile		276

24		5-(3-Nitro-phenyl)-3-phenyl-pyridazine		278
25		3-(6-Phenyl-pyridazin-4-yl)benzoic acid methyl ester		291
26		1-[3-(6-Phenyl-pyridazin-4-yl)-phenyl]-ethanone		275
27		5-(3-Fluoro-phenyl)-3-phenyl-pyridazine		251
28		3-Phenyl-5-(3-trifluoro-methylphenyl)-pyridazine		301
29		5-(3-Methoxy-phenyl)-3-phenyl-pyridazine		263
30		5,2′-Difluoro-5′-(6-phenyl-pyridazin-4-yl)-biphenyl-2-carbonitrile	7.54-7.80 (6H, m), 8.15-8.20 (1H, m), 8.29-8.36 (4H, m), 8.58 (1H, d, *J* 2.3), 9.72 (1H, d, *J* 2.3).	370

				
31		3,2′-Difluoro-5′-(6-phenyl-pyridazin-4-yl)-biphenyl-2-carbonitrile	7.54-7.62 (3H, m), 7.65-7.71 (3H, m), 7.95-8.00 (1H, m), 8.29-8.38 (4H, m), 8.60-8.65 (1H, m), 9.70 (1H, d, *J* 2.4).	370
32		5-(4-Fluoro-3-methoxy-phenyl)-3-phenyl-pyridazine	4.01 (3H, s), 7.25-7.27 (3H, m), 7.52-7.58 (3H, m), 7.94 (1H, d, *J* 2.0), 8.15 (2H, dd, *J* 1.6, 7.8), 9.37 (1H, d, *J* 2.3).	281

EXAMPLE 33

6,2′-Difluoro-5′-[6-(4-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile

5-Chloropyridazin-3-one (22 mg, 0.169 mmol), palladium bis-(diphenylphosphinylbutane)dichloride (10 mg), 6,2′-difluoro-5′-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)biphenyl-2-carbonitrile (50 mg, 0.15 mmol) and 2N Na_2CO_3 (0.3 ml) in toluene (3 ml) were combined and heated to 150°C for 600 s in a Smith Synthesiser microwave reactor. The reaction was diluted with CH_2Cl_2 (6 ml) and H_2O (2 ml) then poured into PTFE (5 μM) fritted syringe barrels. The organic phase was collected,

concentrated and recrystallised from isopropanol to give 29 mg (62%) 6,2′-difluoro-5′-(6-oxo-1,6-dihydropyridazin-4-yl)biphenyl-2-carbonitrile.

The product from above was stirred with triethylamine (20 µl) and *N*-phenyltrifluoromethanesulfonimide (40 mg) in CH_2Cl_2 (5 ml) for 18 h. Further reagents were added and stirring continued for an additional 18 h. The reaction was concentrated and purified by column chromatography using 1:1 ethyl acetate/hexanes as eluent. Trifluoromethanesulfonic acid 5-(2′-cyano-6,6′-difluorobiphenyl-3-yl)pyridazin-3-yl ester was obtained as a yellow oil. *m/z* (ES^+) 442.

The product from above, 4-fluorophenylboronic acid (14 mg), palladium bis(diphenylphosphinylbutane)dichloride (4 mg) and 2N Na_2CO_3 (0.5 ml) in tetrahydrofuran (2 ml) were combined and heated to 150°C for 600 s in a Smith Synthesiser microwave reactor. The reaction was diluted with CH_2Cl_2 (6 ml) and H_2O (2 ml) then poured into a PTFE (5 µM) fritted syringe barrel. The organic phase was collected, concentrated and purified by column chromatography using 1:1 ethyl acetate/hexanes as eluent. The *title compound* was recrystallised from isopropanol to give a colourless solid (3.9 mg). δ_H (400 MHz, d^6 DMSO) 7.42 (2H, t, *J* 8.8), 7.70 (1H, t, *J* 9.2), 7.76-7.87 (2H, m), 7.98 (1H, dd, *J* 1.0, 7.6), 8.34-8.39 (3H, m), 8.35-8.40 (1H, m), 8.45-8.48 (1H, m), 9.69 (1H, d, *J* 2.0); *m/z* (ES^+) 388.

EXAMPLE 34

4-Fluoro-3′-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile

4-Fluoro-3′-(6-oxo-1,6-dihydropyridazin-4-yl)biphenyl-2-carbonitrile (0.35 g, 1.20 mmol) was suspended in phosphorus oxychloride (10 ml) and heated to 70°C for 1 h. The reaction was cooled to room temperature, poured onto ice water and stirred vigorously for 1 h. The beige solid was collected by filtration and azeotroped with methanol to give 3′-(6-chloropyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile (0.24 g). δ_H (400 MHz, d^6 DMSO) 7.73-7.82 (3H, m), 7.83-7.87 (1H, m), 8.04 (1H, dd, *J* 2.7, 9.0),

8.12 (1H, dt, *J* 1.6, 7.8), 8.22 (1H, t, *J* 1.6), 8.40 (1H, d, *J* 2.0), 9.77 (1H, d, *J* 2.0); *m/z* (ES^+) 310.

The product from above (40 mg, 0.129 mmol), benzeneboronic acid (24 mg, 0.197 mmol), tetrakis(triphenylphosphine)palladium(0) and 2N Na_2CO_3 (0.5 ml) in tetrahydrofuran (1.5 ml) were combined and heated to 150°C for 10 min in a Smith Synthesiser microwave reactor. The reaction was diluted with CH_2Cl_2 (6 ml) and NH_4Cl (2 ml) then poured into a PTFE (5 μM) fritted syringe barrel. The organic phase was concentrated while loading onto silica. Column chromatography using 40-50% ethyl acetate/hexanes gave the *title compound* as a white solid (20 mg). δ_H (400 MHz, d^6 DMSO) 7.56-7.62 (3H, m), 7.74-7.80 (3H, m), 7.85-7.89 (1H, m), 8.03-8.06 (1H, m), 8.19 (1H, dt, *J* 1.8, 7.0), 8.29-8.32 (3H, m), 8.58 (1H, d, *J* 2.0), 9.71 (1H, d, *J* 2.0); *m/z* (ES^+) 352.

EXAMPLES 35 TO 70

The compounds in Table 2 were prepared using the requisite boronic acids in an analogous manner to that described in Examples 33 and 34.

Table 2

EX. NO.	PRODUCT	δ_H (400 MHz, d^6 DMSO unless specified otherwise)	*m/z* (ES^+)
35	6,2′-Difluoro-5′-[6-(thien-2-yl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.27 (1H, dd, *J* 4.7, 3.9), 7.71 (1H, t, *J* 9.2), 7.79-7.87 (3H, m), 7.97 (1H, d, *J* 7.0), 8.13 (1H, d, *J* 3.1), 8.33-8.35 (1H, m), 8.41 (1H, dd, *J* 1.2, 4.7), 8.59 (1H, d, *J* 1.2), 9.58 (1H, d, *J* 1.2).	376

36	6,2′-Difluoro-5′-[6-(4-methoxyphenyl)-pyridazin-4-yl]biphenyl-2-carbonitrile	3.86 (3H, s), 7.13 (2H, d, *J* 9.0), 7.69 (1H, t, *J* 9.2), 7.76-7.87 (2H, m), 7.97 (1H, dd, *J* 1.4, 7.6), 8.27 (2H, d, *J* 9.0), 8.32-8.36 (1H, m), 8.45 (1H, dd, *J* 2.3, 6.7), 8.48 (1H, d, *J* 2.0), 9.61 (1H, d, *J* 2.3).	400
37	5′-[6-(3-Chlorophenyl)-pyridazin-4-yl]-6,2′-difluorobiphenyl-2-carbonitrile	7.62-7.63 (2H, m), 7.69-7.73 (1H, m), 7.76-7.87 (2H, m), 7.96 (1H, d, *J* 1.6), 8.28-8.31 (1H, m), 8.36-8.40 (2H, m), 8.48 (1H, dd, *J* 2.5, 6.8), 8.62 (1H, d, *J* 2.0), 9.73 (1H, d, *J* 2.3).	404
38	6,2′-Difluoro-5′-[6-(pyridin-3-yl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.63 (1H, dd, *J* 4.7, 7.8), 7.70-7.88 (3H, m), 7.98 (1H, dd, *J* 1.2, 7.4), 8.36-8.40 (1H, m), 8.49 (1H, dd, *J* 2.3, 6.7), 8.64-8.68 (2H, m), 8.76 (1H, dd, *J* 1.2, 4.7), 9.45 (1H, d, *J* 1.6), 9.76 (1H, d, *J* 2.3).	371
39	5′-[6-(4-Chlorophenyl)-pyridazin-4-yl]-6,2′-difluorobiphenyl-2-carbonitrile	7.56-7.92 (5H, m), 7.98 (1H, dd, *J* 1.2, 7.4), 8.28-8.50 (4H, m), 8.59 (1H, d, *J* 2.3), 9.71 (1H, d, *J* 2.3).	404
40	6,2′-Difluoro-5′-[6-(pyridin-4-yl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.70-7.88 (3H, m), 7.97 (1H, d, *J* 7.4), 8.28 (2H, dd, *J* 1.4, 4.5), 8.37-8.41 (1H, m), 8.49 (1H, dd, *J* 2.5, 6.8), 8.70 (1H, d, *J* 2.3), 8.81-8.84 (2H, m),	371

		9.80 (1H, d, *J* 2.3).	
41	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(4-fluorophenyl)pyridazine	7.42 (2H, t, *J* 9.0), 7.62 (1H, dd, *J* 8.6, 0.8), 8.17-8.22 (1H, m), 8.27-8.39 (4H, m), 8.55 (1H, d, *J* 2.3), 8.75 (1H, d, *J* 2.3), 9.66 (1H, d, *J* 2.3).	382
42	5-[4-Fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-3-(2-fluorophenyl)pyridazine	7.41-7.46 (2H, m), 7.53-7.66 (3H, m), 7.91-8.02 (2H, m), 8.20-8.27 (2H, m), 8.37 (1H, t, *J* 2.0), 8.63-8.64 (1H, m), 9.72 (1H, d, *J* 2.3).	364
43	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)pyridazine	($CDCl_3$): 7.20-7.24 (1H, m), 7.34-7.41 (3H, m), 7.47-7.53 (1H, m), 7.80-7.84 (1H, m), 7.96 (1H, dd, *J* 2.3, 6.7), 8.13 (1H, t, *J* 2.0), 8.19-8.24 (1H, m), 8.52 (1H, d, *J* 2.3), 9.44 (1H, d, *J* 2.0).	382
44	5-[4-Fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-3-(pyridin-3-yl)pyridazine	7.60-7.67 (3H, m), 7.92-7.97 (1H, m), 8.28-8.38 (2H, m), 8.64-8.68 (3H, m), 8.76 (1H, dd, *J* 1.6, 4.7), 9.46 (1H, d, *J* 2.0), 9.74 (1H, d, *J* 2.0).	347
45	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-fluorophenyl)pyridazine	($CDCl_3$): 7.20-7.25 (1H, m), 7.36-7.43 (2H, m), 7.50-7.55 (1H, m), 7.81-8.00 (5H, m), 8.52 (1H, d, *J* 2.3), 9.45 (1H, d, *J* 2.0).	382
46	3-(2,4-Difluorophenyl)-5-[3-(3,5-difluoropyridin-2-	($CDCl_3$): 6.96-7.02 (1H, m), 7.08-7.13 (1H, m), 7.36-7.42	400

	yl)-4-fluorophenyl]-pyridazine	(2H, m), 7.79-7.83 (1H, m), 7.95 (1H, dd, *J* 2.3, 6.3), 8.09 (1H, t, *J* 2.2), 8.23-8.29 (1H, m), 8.52 (1H, d, *J* 2.3), 9.44 (1H, d, *J* 2.3).	
47	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-methoxyphenyl)-pyridazine	($CDCl_3$): 3.93 (3H, s), 7.06-7.09 (1H, m), 7.36-7.47 (3H, m), 7.64 (1H, d, *J* 1.6), 7.79-7.84 (2H, m), 7.97 (1H, dd, *J* 2.3, 6.7), 8.01 (1H, d, *J* 2.3), 8.52 (1H, d, *J* 2.3), 9.43 (1H, d, *J* 2.3).	394
48	6,2′-Difluoro-5′-[6-(2-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.41-7.46 (2H, m), 7.59-7.72 (2H, m), 7.75-7.86 (2H, m), 7.94-8.01 (2H, m), 8.27-8.31 (1H, m), 8.39 (2H, q, *J* 2.1), 9.73 (1H, d, *J* 2.3).	388
49	6,2′-Difluoro-5′-[6-(3-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.38-7.43 (1H, m), 7.61-7.88 (4H, m), 7.96-8.05 (1H, m), 8.13-8.19 (2H, m), 8.35-8.40 (1H, m), 8.48 (1H, dd, *J* 2.5, 6.7), 8.61 (1H, d, *J* 2.1), 9.73 (1H, d, *J* 1.8).	388
50	3-[6-(3-Fluorophenyl)-pyridazin-4-yl]-benzonitrile	7.40-7.45 (1H, m), 7.66 (1H, td, *J* 6.3, 8.0), 7.81 (1H, t, *J* 7.8), 8.04 (1H, dt, *J* 1.2, 7.8), 8.15-8.19 (1H, m), 8.19-8.22 (1H, m), 8.42-8.45 (1H, m), 8.66 (1H, m), 8.67 (1H, d, *J*	276

		2.3), 9.74 (1H, d, *J* 2.3).	
51	3-[6-(2-Fluorophenyl)-pyridazin-4-yl]-benzonitrile	7.43-7.48 (2H, m), 7.60-7.66 (1H, m), 7.80 (1H, t, *J* 7.8), 7.98-8.02 (1H, m), 8.02-8.04 (1H, m), 8.34-8.37 (1H, m), 8.42 (1H, t, *J* 2.0), 8.56-8.57 (1H, m), 9.75 (1H, d, *J* 2.0).	276
52	3-[6-(4-Fluorophenyl)-pyridazin-4-yl]-benzonitrile	7.41-7.47 (2H, m), 7.81 (1H, t, *J* 7.8), 8.02-8.05 (1H, m), 8.37-8.41 (2H, m), 8.41-8.49 (1H, m), 8.62 (1H, d, *J* 2.0), 8.64-8.65 (1H, m), 9.70 (1H, d, *J* 2.0).	276
53	3-[6-(4-Methoxyphenyl)-pyridazin-4-yl]-benzonitrile	3.87 (3H, s), 7.13-7.16 (2H, m), 7.80 (1H, t, *J* 7.8), 8.01-8.04 (1H, m), 8.28-8.31 (2H, m), 8.39-8.42 (1H, m), 8.54 (1H, d, *J* 2.0), 8.62-8.64 (1H, m), 9.62 (1H, d, *J* 2.0).	288
54	3-[6-(3,4-Difluoro-phenyl)pyridazin-4-yl]-benzonitrile	7.69 (1H, td, *J* 8.6, 10.6), 7.82 (1H, t, *J* 7.8), 8.03-8.06 (1H, m), 8.22-8.26 (1H, m), 8.39-8.42 (1H, m), 8.42-8.45 (1H, m), 8.65-8.66 (1H, m), 8.66 (1H, d, *J* 2.0), 9.73 (1H, d, *J* 2.0).	294
55	3-[6-(2,4-Difluoro-phenyl)pyridazin-4-yl]-benzonitrile	7.33-7.38 (1H, m), 7.50-7.56 (1H, m), 7.80 (1H, t, *J* 7.8), 8.20-8.05 (1H, m), 8.08 (1H, td, *J* 7.0, 9.0), 8.34-8.37 (1H,	294

		m), 8.41 (1H, t, *J* 2.0), 8.55-8.57 (1H, m), 9.75 (1H, d, *J* 2.0).	
56	5′-[6-(2-Chlorophenyl)-pyridazin-4-yl]-6,2′-difluorobiphenyl-2-carbonitrile	7.60-7.65 (2H, m), 7.73 (1H, t, *J* 9.1), 7.78-7.90 (2H, m), 7.98-8.05 (1H, m), 8.33 (2H, dd, *J* 1.9, 7.5), 8.36-8.41 (1H, m), 8.50 (1H, dd, *J* 2.3, 6.8), 8.58 (1H, d, *J* 2.1), 9.72 (1H, d, *J* 2.1).	
57	3-(4-Methoxyphenyl)-5-phenylpyridazine	3.86 (3H, s), 7.13 (2H, d, *J* 8.9), 7.56-7.62 (3H, m), 8.02-8.05 (2H, m), 8.25 (2H, d, *J* 8.9), 8.39 (1H, d, *J* 2.1), 9.53 (1H, d, *J* 2.1).	
58	4-Fluoro-3′-[6-(4-methoxy-phenyl)pyridazin-4-yl]-biphenyl-2-carbonitrile	3.86 (3H, s), 7.14 (2H, d, *J* 8.8), 7.73-7.79 (3H, m), 7.85-7.89 (1H, m), 8.03-8.06 (1H, m), 8.17 (1H, dt, *J* 2.0, 7.0), 8.27-8.28 (1H, m), 8.28 (2H, d, *J* 8.8), 8.51 (1H, d, *J* 2.3), 9.63 (1H, d, *J* 2.3).	382
59	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(4-methoxyphenyl)-pyridazine	($CDCl_3$): 3.90 (3H, s), 7.07 (2H, d, *J* 9.0), 7.36-7.41 (2H, m), 7.79-7.82 (1H, m), 7.94-7.96 (2H, m), 8.13 (1H, q, *J* 5.0), 8.12 (1H, d, *J* 9.0), 8.52 (1H, d, *J* 2.3), 9.36 (1H, d, *J* 2.3).	394
60	3-(4-Chlorophenyl)-5-[3-	7.62-7.67 (3H, m), 8.17-8.22	398

	(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-pyridazine	(1H, m), 8.27-8.36 (4H, m), 8.58 (1H, d, *J* 2.0), 8.75 (1H, d, *J* 2.3), 9.68 (1H, d, *J* 2.3).	
61	2-{5-[3-(3,5-Difluoro-pyridin-2-yl)-4-fluoro-phenyl]pyridazin-3-yl}-5-fluorobenzonitrile	($CDCl_3$): 7.36-7.45 (2H, m), 7.50-7.59 (2H, m), 7.84-7.87 (1H, m), 7.99 (1H, dd, *J* 2.3, 6.3), 8.15 (1H, dd, *J* 5.5, 8.6), 8.18 (1H, d, *J* 2,0), 8.51 (1H, d, *J* 2.3), 9.54 (1H, d, *J* 2.3).	398
62	3-(4-Chlorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine	($CDCl_3$): 7.38-7.46 (2H, m), 7.52-7.61 (3H, m), 7.80-7.84 (1H, m), 8.00 (1H, d, *J* 1.6), 8.01 (1H, d, *J* 2.3), 8.11 (2H, d, *J* 8.2), 8.60 (1H, d, *J* 4.3), 9.44 (1H, d, *J* 2.0).	380
63	5-[4-Fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-3-(furan-3-yl)pyridazine	($CDCl_3$): 7.08-7.10 (1H, m), 7.36-7.46 (2H, m), 7.55-7.61 (2H, m), 7.76-7.81 (2H, m), 7.98 (1H, dd, *J* 2.5, 6.5), 8.23 (1H, s), 8.59-8.61 (1H, m), 9.34 (1H, d, *J* 2.3).	336
64	5-[4-Fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-3-(furan-2-yl)pyridazine	($CDCl_3$): 6.63 (1H, q, *J* 1.8), 7.36-7.45 (3H, m), 7.55-7.60 (1H, m), 7.63-7.64 (1H, m), 7.80-7.84 (1H, m), 8.01 (1H, dd, *J* 2.5, 6.5), 8.04 (1H, d, *J* 2.0), 8.59-8.61 (1H, m), 9.34 (1H, d, *J* 2.3).	336
65	3-(2,3-Difluorophenyl)-5-	($CDCl_3$): 7.24-7.45 (4H, m),	382

	[4-fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-pyridazine	7.52-7.60 (1H, m), 7.80-7.84 (1H, m), 7.94-8.02 (2H, m), 8.13 (1H, t, *J* 2.2), 8.59-8.61 (1H, m), 9.48 (1H, d, *J* 2.0).	
66	5-[4-Fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-3-(thien-3-yl)pyridazine	($CDCl_3$): 7.37-7.52 (3H, m), 7.55-7.61 (1H, m), 7.79-7.83 (1H, m), 7.86 (1H, dd, *J* 1.2, 5.1), 7.92 (1H, d, *J* 2.3), 7.99 (1H, dd, *J* 2.3, 6.3), 8.14 (1H, q, *J* 1.4), 8.59-8.61 (1H, m), 9.37 (1H, d, *J* 2.0).	352
67	5-[4-Fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-3-(thien-2-yl)pyridazine	($CDCl_3$): 7.19 (1H, dd, *J* 3.7, 4.9), 7.37-7.46 (2H, m), 7.52-7.61 (2H, m), 7.77-7.82 (2H, m), 7.94 (1H, d, *J* 2.3), 7.99 (1H, dd, *J* 2.5, 6.5), 8.59-8.61 (1H, m), 9.33 (1H, d, *J* 2.0).	352
68	3-(2,5-Difluorophenyl)-5-[4-fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-pyridazine	($CDCl_3$): 7.14-7.23 (2H, m), 7.37-7.45 (2H, m), 7.52-7.60 (1H, m), 7.80-7.84 (1H, m), 7.96-8.01 (2H, m), 8.16 (1H, t, *J* 2.2), 8.59-8.61 (1H, m), 9.47 (1H, d, *J* 2.3).	382
69	3-(3,4-Difluorophenyl)-5-[4-fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-pyridazine	($CDCl_3$): 7.31-7.46 (3H, m), 7.56-7.61 (1H, m), 7.80-7.84 (1H, m), 7.87-7.91 (1H, m), 7.97-8.09 (3H, m), 8.59-8.61 (1H, m), 9.45 (1H, d, *J* 2.3).	382
70	4-{5-[4-Fluoro-3-(3-fluoro-	($CDCl_3$): 7.39-7.47 (2H, m),	371

	pyridin-2-yl)phenyl]-pyridazin-3-yl}-benzonitrile	7.57-7.61 (1H, m), 7.82-7.87 (3H, m), 8.03 (1H, dd, *J* 2.5, 6.5), 8.06 (1H, d, *J* 2.0), 8.28 (1H, s), 8.30 (1H, t, *J* 1.8), 8.59-8.61 (1H, m), 9.51 (1H, d, *J* 2.3).	

EXAMPLE 71

N-[5-(3-Bromophenyl)pyridazin-3-yl]-*N*-methylamine

Lead tetraacetate (363.3 g, 819 mmol) and trifluoroacetic acid (825 ml) were combined and cooled to 0°C before adding 1-bromo-3-vinylbenzene (150 g, 819 mmol) in CH_2Cl_2 (1 l) dropwise so as to maintain a temperature of <10°C. The reaction was then allowed to warm to room temperature and stirred for 2 h. The reaction was diluted with CH_2Cl_2 (500 ml), poured into H_2O (3 l), and stirred vigorously before filtering through a pad of Hyflo. The organic phase was separated and the cake rinsed with a further portion of CH_2Cl_2 (1 l), which was subsequently washed with the separated aqueous phase. The combined organic extracts were washed with H_2O (750 ml), $NaHCO_3$ (750 ml) and H_2O (750 ml), dried over $MgSO_4$ and concentrated to give (3-bromophenyl)acetaldehyde (163 g), which was used directly.

6N HCl (139 ml) was added dropwise to a solution of morpholine (75 ml, 860 mmol) in 1,4-dioxane (1140 ml). On complete addition, glyoxylic acid (72 g, 778 mmol) and the product from above (163 g, 819 mmol) were added and the reaction heated to reflux for 15 h. The reaction was cooled to room temperature, diluted with H_2O (800 ml) and the products extracted into ethyl acetate (2 x 800 ml). The combined organic extracts were washed with brine (125 ml), dried over $MgSO_4$ and concentrated. 4-(3-Bromophenyl)-5-hydroxy-5*H*-furan-2-one was obtained as a cream solid by crystallising from diethyl ether/hexanes (95.6 g). δ_H (360 MHz, d^6

DMSO) 6.64 (1H, d, *J* 8.8), 6.88 (1H, s), 7.48 (1H, t, *J* 8.1), 7.70-7.73 (1H, m), 7.78-7.81 (1H, m), 8.00-8.01 (1H, m), 8.04 (1H, d, *J* 8.8).

The product from above (95.6 g, 375 mmol) and hydrazine hydrate (45.5 ml, 937 mmol) in ethanol (1.9 l) were combined and heated to reflux for 12 h. The reaction was cooled to room temperature, diluted with H_2O (960 ml) and cooled in an ice bath. 5-(3-Bromophenyl)-2*H*-pyridazin-3-one was obtained as a pale yellow solid, which was collected by filtration (34 g). The filtrate was concentrated to a smaller volume and a further 16 g of product was collected by filtration. δ_H (360 MHz, d^6 DMSO) 7.20 (1H, d, *J* 2.1), 7.48 (1H, t, *J* 7.9), 7.70-7.73 (1H, m), 7.81-7.84 (1H, m), 8.04 (1H, t, *J* 1.8), 8.30 (1H, d, *J* 2.1), 13.15 (1H, s).

The product from above (10 g, 39.8 mmol) was suspended in phosphorus oxychloride (60 ml) and heated to 70°C for 3 h. The reaction was concentrated to half the volume before pouring onto ice water and stirring vigorously for 1 h. 5-(3-Bromophenyl)-3-chloropyridazine was obtained as an orange solid, which was collected by filtration and azeotroped with toluene (10.6 g). δ_H (360 MHz, d^6 DMSO) 7.54 (1H, t, *J* 7.9), 7.76-7.79 (1H, m), 7.99-8.02 (1H, m), 8.25 (1H, t, *J* 1.8), 8.35 (1H, d, *J* 2.1), 9.70 (1H, d, *J* 2.1).

The product from above (0.5 g, 1.86 mmol) was added to a 2M solution of methylamine in tetrahydrofuran (3 ml) and heated to 170°C for 1 h in a Smith Synthesiser microwave reactor. The organic phase was diluted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated while loading onto silica. Column chromatography using 50% ethyl acetate/hexanes followed by ethyl acetate as eluent gave the *title compound* as an orange solid (0.1 g). δ_H (360 MHz, d^6 DMSO) 2.92 (3H, d, *J* 4.9), 6.85 (1H, q, *J* 4.9), 7.00 (1H, d, *J* 2.1), 7.49 (1H, t, *J* 7.9), 7.68-7.71 (1H, m), 7.75-7.78 (1H, m), 7.97 (1H, t, *J* 1.8), 8.80 (1H, d, *J* 2.1); *m/z* (ES^+) 264, 266.

EXAMPLES 72 TO 78

The compounds in Table 3 were prepared in an analogous manner to that described in Example 71.

Table 3

EX. NO.	PRODUCT	δ_H (400 MHz, d^6 DMSO)	*m/z* (ES$^+$)
72	*N*-[5-(3-Bromophenyl)-pyridazin-3-yl]-*N*-isopropylamine	1.21 (6H, d, *J* 6.3), 4.13-4.22 (1H, m), 6.70 (1H, d, *J* 7.4), 6.97 (1H, d, *J* 2.1), 7.49 (1H, t, *J* 7.9), 7.68-7.71 (1H, m), 7.72-7.75 (1H, m), 7.93 (1H, t, *J* 1.8), 8.76 (1H, d, *J* 2.1).	292, 294
73	*N*-[5-(3-Bromophenyl)-pyridazin-3-yl]-*N*-cyclopropylamine	0.47-0.51 (2H, m), 0.75-0.80 (2H, m), 2.65-2.73 (1H, m), 7.08 (1H, d, *J* 2.0), 7.33-7.35 (1H, m), 7.50 (1H, t, *J* 7.9), 7.69-7.72 (1H, m), 7.77-7.80 (1H, m), 7.99 (1H, t, *J* 1.8), 8.86 (1H, d, *J* 2.0).	290, 292
74	*N*-Allyl-*N*-[5-(3-bromophenyl)-pyridazin-3-yl]amine	4.04-4.08 (2H, m), 5.10-5.13 (1H, m), 5.22-5.28 (1H, m), 5.93-6.02 (1H, m), 7.04 (1H, d, *J* 2.0), 7.05-7.07 (1H, m), 7.49 (1H, t, *J* 7.8), 7.68-7.71 (1H, m), 7.74-7.77 (1H, m), 7.95 (1H, t, *J* 1.8), 8.82 (1H, d, *J* 2.0).	290, 292
75	*N*-[5-(3-Bromophenyl)-	1.20 (3H, t, *J* 7.0), 3.41 (2H, qd, *J* 5.5, 7.0), 6.84 (1H, t, *J* 5.5),	278, 280

	pyridazin-3-yl]-*N*-ethylamine	6.99 (1H, d, *J* 2.0), 7.49 (1H, t, 7.8), 7.68-7.71 (1H, m), 7.74-7.77 (1H, m), 7.95 (1H, t, *J* 1.8), 8.79 (1H, d, *J* 2.0).	
76	*N*-Benzyl-*N*-[5-(3-bromophenyl)-pyridazin-3-yl]amine	4.64 (2H, d, *J* 5.9), 7.08 (1H, d, *J* 2.0), 7.22-7.26 (1H, m), 7.31-7.35 (2H, m), 7.37-7.42 (3H, m), 7.49 (1H, t, 7.8), 7.68-7.71 (1H, m), 7.73-7.76 (1H, m), 7.94 (1H, t, *J* 2.0), 8.82 (1H, d, *J* 2.0).	340, 342
77	*N*-[5-(3-Bromophenyl)-pyridazin-3-yl]-*N*-(2-methoxybenzyl)-amine	3.85 (3H, s), 4.59 (2H, d, *J* 5.9), 6.87-6.91 (1H, m), 7.00-7.03 (1H, m), 7.11 (1H, d, *J* 2.0), 7.18 (1H, t, *J* 5.9), 7.22-7.29 (2H, m), 7.49 (1H, t, *J* 7.8), 7.68-7.71 (1H, m), 7.73-7.76 (1H, m), 7.93-7.94 (1H, m), 8.81 (1H, d, *J* 2.0).	370, 372
78	5-(3-Bromophenyl)-3-(2,5-dihydropyrrol-1-yl)pyridazine	4.36 (4H, s), 6.09 (2H, s), 7.11 (1H, d, *J* 2.0), 7.50 (1H, t, *J* 7.8), 7.69-7.72 (1H, m), 7.87-7.90 (1H, m), 8.12 (1H, t, *J* 1.8), 8.90 (1H, d, *J* 2.0).	302, 304

EXAMPLE 79

5-(3-Bromophenyl)-3-ethoxypyridazine

Sodium metal (0.13 g, 5.65 mmol) was added portionwise to dry ethanol (10 ml) under external cooling (water bath). On addition of all the sodium, the reaction was allowed to attain room temperature and the solution stirred for 1 h before adding 5-(3-bromophenyl)-3-chloropyridazine (0.15 g, 0.557 mmol) in ethanol (5 ml). The suspension was stirred for 18 h

before adding water and removing the ethanol *in vacuo*. The products were extracted into CH_2Cl_2, dried over $MgSO_4$ and concentrated. The *title compound* was obtained as a white solid following preparative TLC using 25% ethyl acetate/hexanes as eluent (30 mg). δ_H (400 MHz, d^6 DMSO) 1.41 (3H, t, *J* 7.0), 4.55 (2H, q, *J* 7.0), 7.50 (1H, t, *J* 8.0), 7.55 (1H, d, *J* 2.0), 7.71-7.74 (1H, m), 7.91-7.94 (1H, m), 8.14 (1H, t, *J* 1.8), 9.30 (1H, d, *J* 2.0); *m/z* (ES^+) 279, 281.

EXAMPLE 80

3-Allyloxy-5-(3-bromophenyl)pyridazine

Sodium hydride as a 60% dispersion in mineral oil (0.175 g, 4.38 mmol) was added to a solution of allyl alcohol (0.25 ml, 3.79 mmol) in tetrahydrofuran (4 ml) and stirred for 30 min before adding 5-(3-bromophenyl)-3-chloropyridazine (0.5 g, 1.86 mmol). The suspension was heated to 170°C for 30 min in a Smith Synthesiser microwave reactor. The reaction was diluted with ethyl acetate, washed with H_2O, dried over $MgSO_4$ and concentrated while loading onto silica. Column chromatography using 20% ethyl acetate/hexanes as eluent gave the *title compound* as a white solid (0.2 g). δ_H (400 MHz, d^6 DMSO) 5.03-5.05 (2H, m), 5.29-5.32 (1H, m), 5.44-5.50 (1H, m), 6.10-6.20 (1H, m), 7.51 (1H, t, *J* 8.0), 7.61 (1H, d, *J* 2.0), 7.72-7.75 (1H, m), 7.92-7.95 (1H, m), 8.16 (1H, t, *J* 1.8), 9.33 (1H, d, *J* 2.0); *m/z* (ES^+) 291, 293.

EXAMPLE 81

3-(6-Isopropylaminopyridazin-4-yl)benzonitrile

N-[5-(3-Bromophenyl)pyridazin-3-yl]-*N*-isopropylamine (0.1 g, 0.342 mmol), zinc cyanide (52 mg, 0.443 mmol) and tetrakis(triphenylphosphine)palladium(0) (10 mg) were taken up in *N,N*-dimethylformamide (2 ml). The reaction was heated to 150°C for 10 min in a Smith

Synthesiser microwave reactor. The reaction was diluted with CH_2Cl_2 (6 ml) and H_2O (2 ml) then poured into a PTFE (5 μM) fritted syringe barrel. The organic phase was concentrated and purified by column chromatography using 50-75% ethyl acetate/hexanes as eluent. The *title compound* was obtained as a white solid by recrystallising from ethyl acetate (36 mg). δ_H (400 MHz, d^6 DMSO) 1.21 (6H, d, *J* 6.7), 4.13-4.21 (1H, m), 6.76 (1H, d, *J* 7.4), 7.01 (1H, d, *J* 2.0), 7.74 (1H, t, *J* 7.8), 7.95-7.97 (1H, m), 8.05-8.08 (1H, m), 8.25-8.26 (1H, m), 8.81 (1H, d, *J* 2.0); *m/z* (ES^+) 238.

EXAMPLES 82 TO 84

The compounds in Table 4 were prepared in an analogous manner to that described in Example 81.

Table 4

EX. NO.	PRODUCT	δ_H (400 MHz, d^6 DMSO)	*m/z* (ES^+)
82	3-(6-Benzylamino-pyridazin-4-yl)-benzonitrile	4.65 (2H, d, *J* 5.9), 7.13 (1H, d, *J* 1.6), 7.22-7.26 (1H, m), 7.31-7.35 (2H, m), 7.38-7.40 (2H, m), 7.47 (1H, t, *J* 5.9), 7.74 (1H, t, *J* 7.8), 7.94-7.97 (1H, m), 8.06-8.09 (1H, m), 8.26-8.28 (1H, m), 8.87 (1H, d, *J* 1.6).	287
83	3-[6-(2-Methoxy-benzylamino)-pyridazin-4-yl]-benzonitrile	3.84 (3H, s), 4.60 (2H, d, *J* 5.9), 6.87-6.91 (1H, m), 7.00-7.03 (1H, m), 7.16 (1H, d, *J* 2.0), 7.22-7.28 (3H, m), 7.74 (1H, t, *J* 7.8), 7.95-7.97 (1H, m), 8.06-	317

		8.09 (1H, m), 8.26-8.27 (1H, m), 8.86 (1H, d, *J* 2.0).	
84	3-(6-Benzyloxy-pyridazin-4-yl)-benzonitrile	5.59 (2H, s), 7.34-7.38 (1H, m), 7.40-7.44 (2H, m), 7.52-7.55 (2H, m), 7.72 (1H, d, *J* 2.0), 7.76 (1H, t, *J* 7.8), 7.98-8.01 (1H, m), 8.26-8.29 (1H, m), 8.46-8.47 (1H, m), 9.40 (1H, d, *J* 2.0).	288

EXAMPLE 85

3′-(6-Ethylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile

N-[5-(3-Bromophenyl)pyridazin-3-yl]-*N*-ethylamine (0.1 g, 0.360 mmol), 2-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-5-fluorobenzonitrile (0.1 g, 0.429 mmol), 2N Na_2CO_3 (0.5 ml) and tetrakis(triphenylphosphine)-palladium(0) (10 mg) in tetrahydrofuran (1.5 ml) were combined and heated to 150°C for 10 min in a Smith Synthesiser microwave reactor. The reaction was diluted with CH_2Cl_2 (6 ml) and NH_4Cl (2 ml) then poured into a PTFE (5 μM) fritted syringe barrel. The organic phase was concentrated while loading onto silica and purified by column chromatography using 50% ethyl acetate/hexanes followed by ethyl acetate as eluent. The *title compound* was obtained as a white solid by recrystallising from ethyl acetate (46 mg). δ_H (400 MHz, d^6 DMSO) 1.19 (3H, t, *J* 7.0), 3.41 (2H, qd, *J* 5.1, 7.0), 6.88 (1H, t, *J* 5.1), 7.05 (1H, d, *J* 1.6), 7.69-7.76 (3H, m), 7.79-7.83 (1H, m), 7.85-7.88 (1H, m), 7.94-7.95 (1H, m), 8.01-8.04 (1H, m), 8.85 (1H, d, *J* 1.6); *m/z* (ES^+) 319.

EXAMPLES 86 TO 94

The compounds in Table 5 were prepared in an analogous manner to that described in Example 85.

Table 5

EX. NO.	PRODUCT	δ_H (400 MHz, d^6 DMSO)	*m/z* (ES$^+$)
86	4-Fluoro-3′-(6-isopropylamino-pyridazin-4-yl)-biphenyl-2-carbonitrile	1.21 (6H, d, *J* 6.3), 4.14-4.22 (1H, m), 6.74 (1H, d, *J* 7.8), 7.03 (1H, d, *J* 2.0), 7.69-7.76 (3H, m), 7.79-7.82 (1H, m), 7.84-7.86 (1H, m), 7.92-7.94 (1H, m), 8.01-8.04 (1H, m), 8.83 (1H, d, *J* 2.0).	333
87	4-Fluoro-3′-(6-propylaminopyridazin-4-yl)biphenyl-2-carbonitrile	0.95 (3H, d, *J* 7.2), 1.56-1.67 (2H, m), 3.33-3.37 (2H, m), 6.89-6.93 (1H, m), 7.06-7.07 (1H, m), 7.69-7.88 (5H, m), 7.93-7.95 (1H, m), 8.00-8.04 (1H, m), 8.84-8.85 (1H, m).	333
88	3′-(6-Cyclopropyl-aminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile	0.48-0.52 (2H, m), 0.75-0.80 (2H, m), 2.65-2.71 (1H, m), 7.16 (1H, d, *J* 2.0), 7.35-7.37 (1H, m), 7.70-7.76 (3H, m), 7.80-7.84 (1H, m), 7.88-7.91 (1H, m), 7.98-7.99 (1H, m), 8.01-8.04 (1H, m), 8.92 (1H, d, *J* 2.0).	331
89	3′-(6-Allylamino-pyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile	4.04-4.07 (2H, m), 5.09-5.13 (1H, m), 5.23-5.28 (1H, m), 5.93-6.02 (1H, m), 7.07-7.09 (1H, m), 7.10 (1H, d, *J* 1.6), 7.70-7.76 (3H, m), 7.79-7.83 (1H, m), 7.85-	331

		7.88 (1H, m), 7.94-7.95 (1H, m), 8.01-8.04 (1H, m), 8.80 (1H, d, *J* 1.6).	
90	3′-(6-Benzylamino-pyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile	4.64 (2H, d, *J* 5.9), 7.14 (1H, d, *J* 2.0), 7.22-7.26 (1H, m), 7.31-7.35 (2H, m), 7.38-7.41 (2H, m), 7.45 (1H, t, *J* 5.2), 7.69-7.76 (3H, m), 7.78-7.82 (1H, m), 7.84-7.87 (1H, m), 7.92-7.94 (1H, m), 8.01-8.04 (1H, m), 8.89 (1H, d, *J* 2.0).	381
91	4-Fluoro-3′-(6-methylamino-pyridazin-4-yl)-biphenyl-2-carbonitrile	2.92 (3H, d, *J* 5.1), 6.88 (1H, t, *J* 5.1), 7.06 (1H, d, *J* 2.0), 7.69-7.76 (3H, m), 7.79-7.83 (1H, m), 7.86-7.89 (1H, m), 7.95-7.96 (1H, m), 8.00-8.04 (1H, m), 8.87 (1H, d, *J* 2.0).	305
92	4-Fluoro-3′-(6-methoxypyridazin-4-yl)biphenyl-2-carbonitrile	4.09 (3H, s), 7.61 (1H, d, *J* 2.0), 7.70-7.77 (3H, m), 7.82-7.86 (1H, m), 8.01-8.04 (2H, m), 8.13 (1H, t, *J* 1.6), 9.39 (1H, d, *J* 2.0).	306
93	3′-(6-Ethoxypyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile	1.42 (3H, t, *J* 7.0), 4.55 (2H, q, *J* 7.0), 7.59 (1H, d, *J* 2.0), 7.70-7.77 (3H, m), 7.83-7.86 (1H, m), 8.01-8.04 (2H, m), 8.13-8.14 (1H, m), 9.37 (1H, d, *J* 2.0).	320
94	3′-(6-Benzyloxy-pyridazin-4-yl)-4-fluorobiphenyl-2-	5.59 (2H, s), 7.34-7.44 (3H, m), 7.52-7.55 (2H, m), 7.70 (1H, d, *J* 2.0), 7.71-7.77 (3H, m), 7.82-	382

	carbonitrile	7.86 (1H, m), 8.01-8.06 (2H, m), 8.14-8.15 (1H, m), 9.41 (1H, d, *J* 2.0).	

EXAMPLE 95

5-(4-Fluoro-3-hydroxyphenyl)-3-phenylpyridazine

To a solution of 5-(4-fluoro-3-methoxyphenyl)-3-phenylpyridazine (0.6 g, 2.14 mmol) in dichloromethane cooled to -70°C was added boron tribromide (0.81 ml, 8.56 mmol). The reaction mixture was stirred at -70°C for 30 min then allowed to warm to room temperature and stirred for 2 h. The reaction was cooled to 0°C, then 1 ml of methanol was added. The reaction mixture was poured onto a solution of sodium hydrogencarbonate, the precipitate obtained was collected by filtration, washed with water and dried ($MgSO_4$) to give the *title compound* (400 mg). δ_H (400 MHz, $CDCl_3$) 7.37 (1H, dd, *J* 8.4, 11.2), 7.47-7.61 (5H, m), 8.26-8.28 (2H, m), 8.37 (1H, d, *J* 2.0), 9.50 (1H, d, *J* 2.0), 10.25-10.40 (1H, br s); *m/z* (ES^+) 267.

EXAMPLE 96

5-[4-Fluoro-3-(2-methyl-2*H*-[1,2,4]triazol-3-ylmethoxy)phenyl]-3-phenylpyridazine

To a solution of 5-(4-fluoro-3-hydroxyphenyl)-3-phenylpyridazine (80 mg, 0.3 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydride (30 mg, 0.6 mmol). After stirring for 10 min (2-methyl-2*H*-[1,2,4]triazol-3-yl)methanol (50 mg, 0.3 mmol) was added. The reaction mixture was heated at 60°C for 30 min. The reaction mixture was poured into water, and the precipitate obtained was collected by filtration, washed with water and dried ($MgSO_4$). The solid was dissolved in ethyl acetate, adsorbed onto silica and purified by flash chromatography using ethyl

acetate/hexane (20:1) as eluent. The appropriate fractions were combined and evaporated under reduced pressure to give the *title compound* as a solid. δ_H (400 MHz, $CDCl_3$) 4.05 (3H, s), 5.44 (2H, s), 7.27-7.37 (3H, m), 7.51-7.61 (3H, m), 7.92 (2H, dd, *J* 11.3, 2.3), 8.16 (2H, dd, *J* 6.3, 1.6), 9.34 (1H, d, *J* 1.6); *m/z* (ES^+) 362.

EXAMPLE 97

5-[4-Fluoro-3-(1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-ylmethoxy)-phenyl]-3-phenylpyridazine

To a slurry of 5-(4-fluoro-3-hydroxyphenyl)-3-phenylpyridazine (80 mg, 0.3 mmol), (1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-yl)methanol (81 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in tetrahydrofuran (2 ml) was added diisopropyl azodicarboxylate (91 mg, 0.45 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was adsorbed onto silica and purified by flash chromatography using a gradient elution of isohexane/ethyl acetate 20:1 to 1:20 as eluent. The appropriate fractions were combined and evaporated under reduced pressure to give a solid which was recrystallized from acetonitrile to give the *title compound* (45 mg). δ_H (400 MHz, $CDCl_3$) 3.96 (3H, s), 5.21 (2H, s), 7.27-7.34 (3H, m), 7.51-7.61 (4H, m), 7.91 (1H, d, *J* 2.3), 8.13-8.14 (2H, m), 9.35 (1H, d, *J* 2.3); *m/z* (ES^+) 429.

EXAMPLES 98 AND 99

The compounds in Table 6 were prepared in an analogous manner to that described in Example 96.

Table 6

EX.	PRODUCT	δ_H (400 MHz, $CDCl_3$)	*m/z*

NO.			(ES+)
98	5-[4-Fluoro-3-(pyridin-4-ylmethoxy)phenyl]-3-phenylpyridazine	5.27 (2H, s), 7.28-7.34 (3H, m), 7.42 (2H, d, *J* 6.3), 7.51-7.59 (3H, m), 7.88 (1H, d, *J* 2.0), 8.11-8.13 (2H, m), 8.66-8.68 (2H, m), 9.32 (1H, d, *J* 2.0).	358
99	5-[4-Fluoro-3-(pyridin-3-ylmethoxy)phenyl]-3-phenylpyridazine	5.26 (2H, s), 7.27-7.39 (4H, m), 7.51-7.59 (3H, m), 7.83-7.86 (1H, m), 7.90 (1H, d, *J* 2.3), 8.12-8.14 (2H, m), 8.63 (1H, d, *J* 3.9), 8.74 (1H, s), 9.33 (1H, d, *J* 2.0).	358

EXAMPLE 100

5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-4-yl)pyridazine

To 3-chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine (0.2 g, 0.66 mmol) in 1,4-dioxane (2 ml) was added 4-tri-*n*-butylstannylpyridine (0.484 g, 1.31 mmol) followed by tetrakis(triphenylphosphine)palladium(0) (0.076 g, 0.065 mmol) and the mixture heated at 150°C in a Smith Synthesiser microwave reactor for 12 min. The reaction was diluted with dichloromethane, filtered and evaporated to give a brown solid. The crude product was chromatographed on silica eluting with 1-5% methanol/CH_2Cl_2. Appropriate fractions were pooled and evaporated to give the *title compound* as a cream-coloured solid. δ_H (400 MHz, $CDCl_3$) 7.40-7.47 (2H, m), 7.57-7.61 (1H, m), 7.82-7.86 (1H, m), 8.02-8.09 (4H, m), 8.60-8.62 (1H, m), 8.82-8.84 (2H, m), 9.53 (1H, d, *J* 2.3); *m/z* (ES+) 347.

EXAMPLES 101 TO 104

The compounds in Table 7 were prepared using the requisite heterocyclic stannanes in an analogous manner to that described in Example 100 above.

Table 7

EX. NO.	PRODUCT	δ_H (400 MHz, $CDCl_3$)	*m/z* (ES+)
101	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyrazin-2-yl)-pyridazine	7.38-7.46 (2H, m), 7.56-7.61 (1H, m), 7.87-7.92 (1H, m), 8.09 (1H, dd, *J* 2.3, 6.7), 8.59 (1H, m), 8.68-8.75 (3H, m), 9.55 (1H, d, *J* 2.3), 9.97 (1H, d, *J* 1.2).	348
102	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(thiazol-2-yl)pyridazine	7.37-7.46 (2H, m), 7.55-761 (2H, m), 7.86-7.90 (1H, m), 8.02 (1H, d, *J* 3.5), 8.08 (1H, dd, *J* 2.3, 6.7), 8.56 (1H, d, *J* 2.3), 8.59-8.61 (1H, m), 9.49 (1H, d, *J* 2.3).	353
103	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-2-yl)pyridazine	7.54-7.67 (3H, m), 7.92-7.97 (1H, m), 8.05-8.09 (1H, m), 8.24 (1H, s), 8.26 (1H, s), 8.61-8.66 (2H, m), 8.78 (1H, d, *J* 2.3), 8.80 (1H, dd, *J* 0.8, 4.3), 9.77 (1H, d, *J* 2.3).	347
104	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)-phenyl]-3-(3-fluoro-pyridin-2-yl)-pyridazine	7.39-7.46 (2H, m), 7.56-7.61 (1H, m), 7.81-7.85 (1H, m), 8.02 (1H, dd, *J* 2.5, 6.5), 8.23 (2H, s), 8.60 (1H, d, *J* 4.3), 8.67 (2H, dd, *J* 0.8, 7.0), 9.54 (1H, d, *J* 1.6).	365

EXAMPLE 105

5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(1*H*-[1,2,3]triazol-4-yl)pyridazine

A degassed solution of 3-chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)-phenyl]pyridazine (200 mg, 0.66 mmol) was formed in tetrahydrofuran (3 ml). (Trimethylsilyl)acetylene (0.14 ml, 0.99 mmol), triethylamine (0.14 ml, 1 mmol), bis(triphenylphosphine)palladium(II) chloride (23 mg, 0.03 mmol) and triphenylphosphine (4 mg, 0.015 mmol) were added in that order and the mixture left to stir for 20 min at room temperature. Copper(I) iodide (2 mg, 0.01 mmol) was added and the mixture stirred at room temperature for 18 h. The solvent was removed and the residue purified by flash column chromatography over silica using 80% ethyl acetate:20% isohexane as eluent to give 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-trimethylsilanylethynylpyridazine as a brown solid (210 mg). δ_H (400 MHz, $CDCl_3$) 0.31 (9H, s), 7.34-7.45 (2H, m), 7.55-7.60 (1H, m), 7.74-7.78 (1H, m), 7.79 (1H, d, *J* 2.3), 7.95 (1H, dd, *J* 2.5, 6.5), 8.58-8.61 (1H, m), 9.39 (1H, d, *J* 2.3).

Sodium azide (19 mg, 0.29 mmol) was added to a solution of 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-trimethylsilanylethynylpyridazine (100 mg, 0.26 mmol) in *N,N*-dimethylformamide (1 ml) and the mixture stirred at room temperature for 16 h, then at 70°C for 4 h. The reaction mixture was allowed to cool to room temperature and was added to water (20 ml) then extracted with ethyl acetate (5 x 10 ml). The combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated to a brown solid. Purification by preparative thin-layer chromatography using 10% methanol:90% dichloromethane as eluent gave the *title compound* as a tan solid. δ_H (400 MHz, d^6-DMSO) 7.63 (1H, t, *J* 9.8), 8.16-8.27 (3H, m), 8.49 (1H, d, *J* 2.3), 8.69 (1H, s), 8.75 (1H, d, *J* 2.3), 9.66 (1H, d, *J* 2.0); *m/z* (ES^+) 355.

EXAMPLE 106

5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine-3-carboxylic acid ethyl ester

A solution of 3-chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-pyridazine (100 mg, 0.33 mmol) was formed in ethanol (10 ml) with *N,N*-dimethylformamide (2 ml). Sodium acetate (54 mg, 0.66 mmol) was added and the mixture degassed with nitrogen. [1,1'-Bis(diphenylphosphino)-ferrocene]palladium(II) chloride (1:1 complex with dichloromethane) (20 mg, 0.03 mmol) was added and carbon dioxide was bubbled through the solution as the mixture was heated to 90°C and maintained at that temperature for 45 min. The mixture was allowed to cool to room temperature and the solvent was removed. The residue was purified by flash column chromatography over silica, using 80% ethyl acetate:20% isohexane as eluent, then recrystallisation from dichloromethane and isohexane, to give the *title compound* as a white solid (30 mg). δ_H (400 MHz, $CDCl_3$) 1.51 (3H, t, *J* 7.0), 4.59 (2H, q, *J* 7.2), 7.38-7.46 (2H, m), 7.55-7.61 (1H, m), 7.81-7.86 (1H, m), 8.03 (1H, dd, *J* 2.5, 6.5), 8.41 (1H, d, *J* 2.3), 8.59-8.61 (1H, m), 9.62 (1H, d, *J* 2.3); *m/z* (ES^+) 342.

EXAMPLE 107

5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)-pyridazine-1-oxide

To a mixture of 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)pyridazine (50 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was added *m*-chloroperbenzoic acid (50%; 68 mg, 0.20 mmol). The solution was left to stand at room temperature for 22 h. 10% Sodium carbonate solution (1 ml) was added and the solution poured into a PTFE (5 μM) fritted syringe barrel. The organic phase was evaporated and the crude product purified by preparative TLC using a solvent system of 5% methanol in CH_2Cl_2 to

yield a white solid. The solid was further purified by prep HPLC using a solvent system of 30-80% acetonitrile in 0.1% trifluoroacetic acid in water. Appropriate fractions were combined to give the *title compound* as a white solid (3 mg). δ_H (400 MHz, $CDCl_3$) 7.19-7.25 (1H, m), 7.29-7.41 (3H, m), 7.47-7.53 (1H, m), 7.73-7.76 (1H, m), 7.78 (1H, t, *J* 1), 7.91 (1H, dd, *J* 3, 7), 8.06-8.10 (1H, m), 8.42 (1H, d, *J* 1), 8.51 (1H, d, *J* 2); *m/z* (ES^+) 398.

EXAMPLE 108

3-(2,6-Difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine

To a degassed mixture of 3-chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine (0.25 g, 0.82 mmol), hexamethylditin (0.323 g, 0.98 mmol) and lithium chloride (0.1024 g, 2.46 mmol) in 1,4-dioxane (12 ml) was added tetrakis(triphenylphosphine)palladium(0) (0.048 g, 0.041 mmol) and the mixture heated at 100°C for 3 h. Mass spectroscopy showed formation of the intended stannane. 1-Bromo-2,6-difluorobenzene (0.3177 g, 0.187 ml, 1.65 mmol) was added, followed by tetrakis(triphenylphosphine)palladium(0) (0.01 g, 0.0082 mmol), and the mixture heated at 100°C for 6 h. The reaction was cooled to room temperature, filtered and evaporated and the crude product purified by preparative TLC (2 plates; 4% methanol-CH_2Cl_2). Appropriate bands were collected and processed to give the *title compound* as an off-white solid which was recrystallised from ethyl acetate/isohexane to give a white solid (42 mg). δ_H (400 MHz, $CDCl_3$) 7.05-7.12 (2H, m), 7.32-7.59 (4H, m), 7.79-7.85 (2H, m), 8.00 (1H, dd, *J* 2.5, 6.5), 8.58-8.60 (1H, m), 9.51 (1H, d, *J* 2.3).